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ATTORNEYS AT LAW

Docket No.: 244118US0CONT

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Application Serial No.: 10/692,738
Patent No.: 6,908,905
Applicants: Koji OHSUMI, et al.
Filing Date: October 27, 2003
For: N-SUBSTITUTED PYRAZOLE-O-GLYCOSIDE DERIVATIVES AND THERAPEUTIC AGENT FOR DIABETES CONTAINING THE SAME
Group Art Unit: 1623
Examiner: JOHNSEN, J.H.

SIR:

Attached hereto for filing are the following papers:

**Petition Under 37 C.F.R. §1.705(d) and Request for Reconsideration of Patent Term Adjustment with Exhibits A-G**

Our credit card payment form in the amount of **$200.00** is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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Docket No.: 244118US0CONT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

| | |
|---|---|
| IN RE APPLICATION OF: | : EXAMINER: JOHNSEN, J. H. |
| KOJI OHSUMI ET AL | : GROUP ART UNIT: 1623 |
| SERIAL NO.: 10/692,738 | : U.S. PATENT NO.: 6,908,905 |
| FILED: OCTOBER 27, 2003 | : ISSUED: JUNE 21, 2005 |

FOR: N-SUBSTITUTED PYRAZOLE-O-GLYCOSIDE DERIVATIVES AND THERAPEUTIC AGENT FOR DIABETES CONTAINING THE SAME

PETITION UNDER 37 C.F.R. §1.705(d) AND
REQUEST FOR RECONSIDERATION OF PATENT TERM ADJUSTMENT

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

SIR:

Petitioners hereby request reconsideration of the final patent term adjustment for U.S. Patent No. 6,908,905 of 0 days and, in place thereof, reinstatement of the 44-day patent term adjustment that was indicated on the Notice of Allowance. Petitioners contend that the Office erred in determining that the properly owed 44-day patent term adjustment was exhausted by Applicant delay subsequent to issuance of a Notice of Allowance. The facts of this case are as follows.

Preliminary Matters – Patent Term Adjustment indicated in the Notice of Allowance:

On February 9, 2005, a Notice of Allowance was issued in U.S. Application Serial No. 10/692,738, which indicated that the determination of patent term adjustment under 35 U.S.C. §154(b) was 44 days. The following facts are relevant to the determination by the Office set forth in the Notice of Allowance. The following summary is provided to ensure compliance

with 37 C.F.R. §1.705(b) (referenced by appropriate section 37 C.F.R. §1.705(d)). For ease of reference, Petitioners have indexed the relevant facts by section number:

1) The Office failed to take certain actions within specified time frames under 37 C.F.R. §§1.702(a) and 1.703(a).

   a. The present application was filed on October 27, 2003, and a Notice of Allowance was issued on February 9, 2005. No action under 35 U.S.C. §132 was issued. The time period for the Office's mailing the Notice of Allowance exceeded the 14-month guarantee of 37 C.F.R. §1.702(a)(1) and 37 C.F.R. §1.703(a)(1) by 44 days. As such, a positive patent term adjustment of 44 days is credited to Petitioners.

   b. An appeal was not filed in the present application and, therefore, the following paragraphs do not apply:

      i. 37 C.F.R. §1.702(a)(2)-(3),

      ii. 37 C.F.R. §1.702(e),

      iii. 37 C.F.R. §1.703(a)(4)-(5).

   c. The present application was a first action allowance and, therefore, the following paragraphs do not apply:

      i. 37 C.F.R. §1.703(a)(2)-(3),

   d. 37 C.F.R. §§1.702(a)(4) and 1.703(a)(6) does not apply at this juncture since these guarantees relate to post-allowance proceedings (see below).

2) A patent was issued within 3 years of actual filing of the present application. Therefore, no delay is present under 37 C.F.R. §§1.702(b) and 1.703(b) that would result in a patent term adjustment.

3) There was no interference proceeding conducted in the present application. Therefore, no delay is present under 37 C.F.R. §§1.702(c) and 1.703(c) that would result in a patent term adjustment.

4) The present application was not placed under a secrecy order. Therefore, no delay is present under 37 C.F.R. §§1.702(d) and 1.703(d) that would result in a patent term adjustment.

5) As stated in (1)(b) above, no appeal was commenced in the present application. Therefore, no delay is present under 37 C.F.R. §§1.702(e) and 1.703(e) that would result in a patent term adjustment.

6) The present application was not subject to a Terminal Disclaimer, which would eliminate the patent term adjustment arising from (1) – (5) above. As such, no negative alteration of the patent term adjustment is necessary.

7) There were no circumstances preceding mailing of a Notice of Allowance constituting a failure to engage in reasonable efforts to conclude processing or examination of such application as set forth in 37 C.F.R. § 1.704. Therefore, there are no circumstances that would reduce the patent term adjustment arising from (1) – (5) above.

8) The patent term adjustment assessed by the Office based on (1) – (7) above and set forth in the Notice of Allowance in accordance with 37 C.F.R. §1.705(a) was 44 days.

9) The calculated patent term adjustment reflected in the Notice of Allowance was undisputed prior to the payment of the Issue Fee on May 9, 2005.

Accordingly, in view of the foregoing and in accordance with 37 C.F.R. §1.705(b)-(e), Petitioners have agreed to the 44-day patent term adjustment under 35 U.S.C. §154(b) set forth in the Notice of Allowance mailed on February 9, 2005.

Grounds for Request for Reconsideration and Reinstatement of Patent Term Adjustment:

Despite the fact that the Notice of Allowance mailed on February 9, 2005, indicated that the present application is entitled to a 44-day patent term adjustment, U.S. 6,908,905 issued on June 21, 2005, indicates that the patent in question is subject to a 0-day term adjustment. Petitioners respectfully request reconsideration of this final assessment of the patent term adjustment and reinstatement of the 44-day patent term adjustment.

Petitioners submit that the Office has improperly classified the Letter to PTO and supplementary European Search Report filed on May 5, 2005 (copy **enclosed herewith** as Exhibit A), as an "other" paper within the context of 37 C.F.R. §1.704(c)(10). Further, Petitioners assert that the submission of these documents on May 5, 2005, is not a "failure to engage in reasonable efforts to conclude processing or examination of an application" as contemplated by both the statute and the rules of patent practice as the patent issuance process was not delayed in any manner. In addition, Petitioners submit that the Office should

reconsider the patent term adjustment on the grounds that their submission on May 5, 2005, was within the spirit of the 37 C.F.R. §1.704(d) exception.

At the outset, it should be noted that the relevant guarantee to post-allowance proceedings in relation to patent term adjustment is that enunciated in 37 C.F.R. §§1.702(a)(4) and 1.703(a)(6). In these sections, the Office is compelled to issue a patent within four months of the date upon which the Issue Fee is paid. In this case, the Issue Fee was timely paid on May 9, 2005, and the patent issued 43 days later on June 21, 2005. As such, no delay in issuance of the patent occurred. Thus, no positive term adjustment in addition to that set forth in the Notice of Allowance is required.

However, the Office has eliminated the 44-day patent term adjustment. The apparent basis for this alteration in the patent term adjustment can be found in the Patent Term Adjustment History available through the Office's PAIR system (see **attached copy** as Exhibit B). In the Patent Term Adjustment History, the Office has indicated that an Applicant Delay of 48 days has exhausted the previously available patent term adjustment of 44 days.

The only way that any potential positive patent term adjustment may be shortened is by subtracting one day for each day beyond the shortened statutory period that was necessary to file a suitable response to an action or in which the applicant is responsible for failing to "engage in reasonable efforts to conclude processing or examination" of the present application (37 C.F.R. §1.704). To this end, the only paragraph that would apply to result in a negative patent term adjustment following issuance of a Notice of Allowance is 37 C.F.R. §1.704(c)(10), which states:

> (10) Submission of an amendment under § 1.312 or other paper after a notice of allowance has been given or mailed, in which case the period of adjustment set forth in § 1.703 shall be reduced by the *lesser* of:
>
> (i) The number of days, if any, beginning on the date the amendment under § 1.312 or other paper was filed and ending on the mailing date of

> the Office action or notice in response to the amendment under § 1.312 or such other paper; or
>
> (ii) Four months;

In the present application, a Letter to PTO along with a supplementary European Search Report (issued on March 30, 2005) was filed on May 5, 2005. The time period from the date of filing the Letter to PTO and supplementary European Search Report (May 5, 2005) and issuance of U.S. 6,908,905 (June 21, 2005) was 48 days. Based on the Patent Term Adjustment History, it appears that the Office has classified this filing as an "other" paper for purposes of 37 C.F.R. §1.704(c)(10).

As stated above, Petitioners submit that the Office has improperly classified the Letter to PTO and supplementary European Search Report as an "other" paper within the context of 37 C.F.R. §1.704(c)(10). Further, Petitioners assert that the submission of the same on May 5, 2005, is not a "failure to engage in reasonable efforts to conclude processing or examination of an application" as contemplated by both the statute and the rules of patent practice as the patent issuance process was not delayed in any manner. In addition, Petitioners submit that the Office should reconsider the patent term adjustment on the grounds that their submission on May 5, 2005, was within the spirit of the 37 C.F.R. §1.704(d) exception.

*The May 5, 2005, filing is not an "other" paper within the context of 37 C.F.R. §1.704(c)(10)-*

37 C.F.R. §1.704(c)(10) is silent as to what constitutes an "other" paper for purposes of that paragraph. Inspection of the Changes To Implement Patent Term Adjustment Under Twenty-Year Patent Term; Final Rule (65 FR 56566, Sept. 18, 2000, effective Oct. 18, 2000) provides some insight. On page 56373, the Final Rule sets forth, in relevant part: "The submission of amendments (or other papers) after an application is allowed causes substantial interference with the patent issue process... Thus, to continue to permit applicants to submit an

amendment or other paper after a notice of allowance is mailed or given, the Office must establish submission of such papers as circumstances that constitute a failure of an applicant to engage in reasonable efforts to conclude processing or examination of an application."

Unfortunately, the Final Rule did not provide a list of papers that cause "substantial interference." However, Nicholas P. Godici, Acting Under Secretary of Commerce for Intellectual Property and Acting Director of the United States Patent and Trademark Office did so in a subsequent publication entitled "*Clarification of 37 CFR 1.704(c)(10)—Reduction of Patent Term Adjustment for Certain Types of Papers Filed After a Notice of Allowance has been Mailed*," (1247 *Off. Gaz. Pat. Office* 111, 112 (June 26, 2001), copy **enclosed herewith** as Exhibit C; adopted by the Revision of Patent Term Extension and Patent Term Adjustment Provisions; Final Rule ((69 FR 21704, Apr. 22, 2004, effective May 24, 2004)).

In the aforementioned statement by Acting Director Godici, several types of papers were highlighted that *do not cause substantial interference and delay* in the patent issue process and *are not* considered a "failure to engage in reasonable efforts" to conclude processing or examination of an application. These papers include: (1) Issue Fee Transmittal (PTOL-85B), (2) Power of Attorney, (3) Power to Inspect, (4) Change of Address, (5) Change of Status (small/not small entity status), (6) a response to the examiner's reasons for allowance, and (7) letters related to government interests (*e.g.*, those between NASA and the Office).

In contrast, Acting Director Godici indicated that the submission of other papers after a "Notice of Allowance" is mailed that *do cause substantial interference and delay* in the patent issue process and that *are* considered a "failure to engage in reasonable efforts" to conclude processing or examination of an application pursuant to 37 CFR §1.704(c)(10) include: (1) a request for a refund, (2) a status letter, (3) amendments under 37 CFR §1.312, (4) late priority

claims, (5) a certified copy of a priority document, (6) drawings, (7) letters related to biological deposits, and (8) oaths or declarations.

The papers in question in the present application (*i.e.*, the Letter to PTO and the supplementary European Search Report) are not represented in the list of examples provided by Acting Director Godici. However, it is possible to determine by analogy into which category the papers filed on May 5, 2005, would fall.

From the foregoing, it can be ascertained that the documents that are *not* considered to cause a substantial interference and delay are those relating to formal or ministerial matters not requiring Examiner intervention and/or substantive action by the Office. The only exception is a response to the examiner's reasons for allowance, which is easily explained in that the Applicants only opportunity to correct an erroneous statement by the Examiner in the Notice of Allowance occurs after mailing of the same. In contrast, the documents that are considered to cause a substantial interference and delay are those requiring further action by the Office beyond formal or ministerial activities. More specifically, the documents that are considered to cause a substantial interference and delay generally require that the application be remanded to the Examiner for further action.

In the present application, the Letter to PTO and the supplementary European Search Report filed on May 5, 2005 (see Exhibit A) would fall into the former category (*i.e.*, documents that do *not* cause a substantial interference and delay). In other words, the documents filed on May 5, 2005, did not require that the application be remanded to Examiner and were only a matter of form and/or a ministerial act.

The foregoing is clearly manifest in the text of the Letter to PTO filed on May 5, 2005 (see Exhibit A) in which Petitioners clearly expressed the circumstances surrounding the supplementary European Search Report and their intent only to make the document of record.

Specifically, in the Letter to PTO, Petitioners stated that the reference cited in the supplementary European Search Report (EP 1 364 957) did not have an effective publication date so as to constitute "prior art" under U.S. patent law[1]. Moreover, the Letter to PTO also indicated that EP 1 364 957 corresponds to WO 02/068439, which was cited during prosecution of the present application[2] and considered by the Examiner. Accordingly, the Letter to PTO and the supplementary European Search Report did not require any action by Office other than to simply match the documents with the file, which the Office's PAIR system shows occurred without delay. In fact, the determination that the documents filed on May 5, 2005, are purely ministerial was already made by the Office. This determination is evidenced by the fact that the Office did not remand the application back to the Examiner for further action following receipt of the Letter to PTO and the supplementary European Search Report filed on May 5, 2005 (see Exhibit D).

In view of the foregoing, Petitioners submit that the Letter to PTO and the supplementary European Search Report filed on May 5, 2005, are consistent with what the Office considers documents submitted after notice of allowance that *do not cause substantial interference and delay* in the patent issue process. On this ground, Petitioners request reconsideration of the 0-day patent term adjustment and subsequent reinstatement of the 44-day patent term adjustment.

*The May 5, 2005, filing is not a failure to engage in reasonable efforts to conclude processing-*

Further to the foregoing, Petitioners contend that submission of the Letter to PTO and the supplementary European Search Report on May 5, 2005, is not a "failure to engage in

[1] EP 1 364 957 was published on November 26, 2003, while the present application is a continuation (by-pass) of PCT/JP02/04238, filed on April 26, 2002.
[2] Cited on Form PTO-1449 filed on January 27, 2004, considered by the Examiner and attached to Notice of

reasonable efforts to conclude processing or examination of an application" as contemplated by both the statute and the rules of patent practice as the patent issuance process was not delayed in any manner. Petitioners note that the procedure followed by the Office further underscores the argument above and evidences the Office's treatment of the documents filed on May 5, 2005, as being documents relating to formal or ministerial matters.

The intent of the rules relating to patent term adjustments was to safeguard Applicants from delays caused by the Office arising from internal inefficiencies. Mindful of the potential consequences of Applicants intentional acts or contributions to prosecution delays, Congress established that Applicants delays or acts that may result in delays would be subtracted away from any potential term adjustment arising from Office's lack of diligence. To bring into effect this intent, the Director was given power to establish rules and documents relating to when Applicants have failed to engage in reasonable efforts to conclude processing or examination of an application.

In the Final Rule (65 FR 56566, Sept. 18, 2000) establishing the patent term adjustment rules, the Office set forth, "the submission of amendments (or other papers) after an application is allowed causes substantial interference with the patent issue process." This statement was further clarified by Acting Director Godici (see Exhibit C). As stated above, documents that relate to formal or ministerial matters are considered not to cause substantial interference or delay with the patent issue process. As such, when documents related to formal or ministerial matters are filed the patent issuance process continues in an efficient manner straight to issuance without delay.

In the present application, as evidenced by the **enclosed copy** of the Transaction History for the present application as provided by the Office's PAIR system (see Exhibit D), the

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Allowance mailed February 9, 2005.

documents in question were filed on May 5, 2005, and the Issue Fee was paid four (4) days later on May 9, 2005. Nine (9) days after payment of the Issue Fee (13 days after filing the documents in question) the Application was "considered ready for issue" and forward to publications. The next day (May 19, 2005) the application was received in publications and queued for issuance. U.S. patent 6,908,905 issued on June 21, 2005, a mere 43 days after payment of the Issue Fee.

37 C.F.R. §§1.702(a)(4) and 1.703(a)(6) compel the Office to issue a patent within four months of the date upon which the Issue Fee is paid. From the foregoing, it is clear that the Office met this guarantee by greater than two and a half months. It is also clear that the Office did not remand this application to the Examiner to act on the papers filed on May 5, 2005, and that the patent issue process was unaffected by this filing.

Accordingly, Petitioners submit that the Letter to PTO and the supplementary European Search Report filed on May 5, 2005, did not actually any delay, much less substantial interference and delay, in the patent issuance process. On this additional ground, Petitioners request reconsideration of the 0-day patent term adjustment and subsequent reinstatement of the 44-day patent term adjustment.

*The 37 C.F.R. §1.704(d) exception should be adopted for the May 5, 2005, filing-*

Finally, Petitioners requests that the Office adopt the exception set forth in 37 C.F.R. §1.704(d) and reinstate the 44-day patent term adjustment.

37 C.F.R. §1.704(d) provides that a paper containing only an information disclosure statement in compliance with 37 C.F.R. §§1.97 and 1.98 will not be considered (result in a reduction) under 37 C.F.R. §1.704 (c)(10) if it is accompanied by a certification that each item of information contained in the information disclosure statement was cited in a communication

from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of the information disclosure statement.

This provision is intended to permit Applicants to submit information cited in a communication from a foreign patent office in a counterpart application to the Office without a reduction in patent term adjustment if an information disclosure statement is promptly (within thirty days of receipt of the communication) submitted to the Office. In other words, this provision is an attempt to promote prompt disclosure without further punishment to conscientious Applicants.

It is in this very spirit that Petitioners submitted the supplementary European Search Report on May 5, 2005. It is true that Petitioners did not file the supplementary European Search Report in a form in compliance with 37 C.F.R. §§1.97 and 1.98; however, submission in this form was unnecessary since, as explained above, EP 1 364 957 cited therein can not be considered "prior art." Nonetheless, in keeping with the intention of 37 C.F.R. §§1.56, 1.97 and 1.98, Petitioners submitted the supplementary European Search Report to ensure that the record was complete. To punish such a conscientious act is a contradiction to the intent of the rules relating to patent term adjustments.

Petitioners submit the following in regard to the requirement in 37 C.F.R. §1.704(d) that the information disclosure statement was cited in a communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of the information disclosure statement.

On March 30, 2005, the European Patent Office (EPO) issued a supplementary European Search Report (see Exhibit A) in the corresponding European application (EP 02 72

2839), which was sent to Petitioners' European counsel (Mewburn Ellis, LLP). On April 12, 2005, Petitioners' Japanese counsel (Nakamura & Partners) received the supplementary European Search Report forwarded from Mewburn Ellis, LLP (copy **enclosed** as Exhibit E). Petitioners' Japanese counsel then forwarded the supplementary European Search Report to the undersigned, which was received on May 2, 2005 (copy **enclosed** as Exhibit F). In addition, Petitioners' Japanese counsel then forwarded the supplementary European Search Report to Petitioners, which was received on May 10, 2005 (copy **enclosed** attached to Declaration executed by Mr. Masakazu Sugimoto, which also explains the protocol by which multi-national prosecution is commenced by Petitioners, see Exhibit G).

Petitioners submit that no party having an obligation under 37 C.F.R. §1.56(c) had knowledge or came into possession of the supplementary European Search Report more than 30 days before filing of the same in the U.S. Patent Office. Petitioners' European counsel received the communication from the EPO more than 30days prior to the filing of the supplementary European Search Report; however, they are not a party listed in 37 C.F.R. §1.56(c). Specifically, Petitioners' European counsel is not given any authority and responsibility for the prosecution of the present application in front of the U.S. Patent Office and, therefore, is under no obligation to disclose information directly to the Office. However, foreign patent attorneys do have the following duty.

*Gemveto Jewelry Co. v. Lambert Bros., Inc.*, 542 F. Supp. 933, 216 USPQ 976 (S.D. N.Y. 1982), cited in MPEP 2001.06(a), states that only those individuals designated in 37 C.F.R. §1.56 have a duty of disclosure of all material information they are *aware* of regardless of the source of or how they become aware of the information. However, this ruling only prohibits those who have duty of disclosure from escaping responsibility for fraud or

inequitable conduct by keeping the information unfavorable to patentability at foreign patent attorney. Petitioners' European and Japanese counsel acted in good faith and without delay.

In view of the foregoing, Petitioners submit that they have complied with the spirit of 37 C.F.R. §1.704(d) and that full compliance is unreasonable under the circumstances as the reference in question is not prior art. Moreover, Petitioners note that they are in full compliance with the time limit (30 days) for filing the supplementary European Search Report. Therefore, for this additional ground, Petitioners request reconsideration of the 0-day patent term adjustment and subsequent reinstatement of the 44-day patent term adjustment.

In accordance with the provisions of 37 C.F.R. §1.704(b) and (d), Petitioners submit herewith the requisite fee under 37 C.F.R. §1.18(e). In the event that the Office determines that additional fees are required, it is requested that any underpayment be charged to their undersigned Representative's deposit account (Deposit Account No. 15-0030).

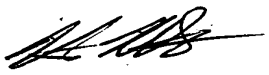
Finally, Petitioners note that 37 C.F.R. §1.704(d) requires any request for reconsideration of patent term adjustment to be filed within two months of the date the patent issued. In this case, U.S. 6,908,905 was issued on June 21, 2005. Two months hence would be August 21, 2005, which was a Sunday. 37 C.F.R. 1.7(a) provides: "Whenever periods of time are specified in this part in days, calendar days are intended. When the day, or the last day fixed by statute or by or under this part for taking any action or paying any fee in the United States Patent and Trademark Office falls on Saturday, Sunday, or on a Federal holiday within the District of Columbia, the action may be taken, or the fee paid, on the next succeeding business day which is not a Saturday, Sunday, or a Federal holiday." Accordingly, the foregoing Petition being filed on Monday, August 22, 2005, (*i.e.*, the next succeeding business day after the date an action is due) is timely.

For the foregoing reasons, Petitioners respectfully submit that the Request for Reconsideration of the Patent Term Adjustment of U.S. 6,908,905 should be GRANTED and the 44-day patent term adjustment assessed in the Notice of Allowance should be reinstated.

Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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ATTORNEYS AT LAW

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Application Serial No.: 10/692,738
Applicants: Koji OHSUMI, et al.
Filing Date: October 27, 2003
For: N-SUBSTITUTED PYRAZOLE-O-GLYCOSIDE DERIVATIVES AND THERAPEUTIC AGENT FOR DIABETES CONTAINING THE SAME
Group Art Unit: 1623
Examiner: Johnsen, J.H.
Allowed: February 9, 2005

SIR:

Attached hereto for filing are the following papers:

**Letter to PTO**
**Supplementary European Search Report**
**Cited Reference - EP 1 364 957 A1**

Our check in the amount of **$0.00** is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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DOCKET NO: [illegible]118US0CONT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

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| IN RE APPLICATION OF | : |
| KOJI OHSUMI, ET AL. | : EXAMINER: JOHNSEN, J. H. |
| SERIAL NO: 10/692,738 | : ART UNIT: 1623 |
| FILED: OCTOBER 27, 2003 | : ALLOWED: FEBRUARY 9, 2005 |

FOR: N-SUBSTITUTED PYRAZOLE-O-GLYCOSIDE DERIVATIVES AND THERAPEUTIC AGENT FOR DIABETES CONTAINING THE SAME:

LETTER TO PTO

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

Applicants wish to make of record the enclosed Supplemental European Report issued on March 30, 2005 in a corresponding foreign application. In the Supplemental European Report, the European Search Authority identifies EP 1 364 957 as a patent of interest but notes that it is "an earlier patent document, but published on, or after the filing date" of the corresponding foreign application. Indeed, EP 1 364 957 published on November 26, 2003, while the above-identified application is a continuation of PCT/JP02/04238, filed on April 26, 2002. Therefore, EP 1 364 957 is not "prior art" for the present application. Further, Applicants note that EP 1 364 957 corresponds to International Publication No. WO 02/068439 (published September 6, 2002), which was cited in the present application on January 27, 2004, and was acknowledged as having been considered by the Examiner on February 9, 2005.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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Datum/Date
30.03.05

| Zeichen/Ref./Réf. | Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°. |
|---|---|
| KMN/FP6187793 | 02722839.4-2101-JP0204238 |
| Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire: Ajinomoto Co., Inc. | |

# COMMUNICATION

The European Patent Office herewith transmits as an enclosure the European search report for the above-mentioned European patent application.

If applicable, copies of the documents cited in the European search report are attached.

[X] Additional set(s) of copies of the documents cited in the European search report is (are) enclosed as well.

## REFUND OF THE SEARCH FEE

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European Patent Office

# SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 02 72 2839

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.7) |
|---|---|---|---|
| E | EP 1 364 957 A (KISSEI PHARMACEUTICAL CO., LTD) 26 November 2003 (2003-11-26)<br>* page 37 - page 39 * | 1 | C07H17/02<br>A61K31/7056<br>A61P3/10 |

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07H
A61K

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| Munich | 18 March 2005 | Bardili, W |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

1

EPO FORM 1503 03.82 (P04C04)

# ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 72 2839

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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18-03-2005

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 1364957 A | 26-11-2003 | CA 2438593 A1 | 06-09-2002 |
| | | EP 1364957 A1 | 26-11-2003 |
| | | US 2004132669 A1 | 08-07-2004 |
| | | WO 02068439 A1 | 06-09-2002 |
| | | TW 593329 B | 21-06-2004 |

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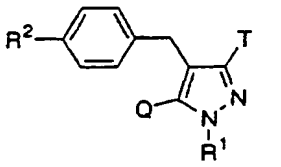
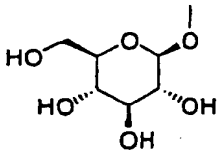
# (54) GLYCOPYRANOSYLOXYPYRAZOLE DERIVATIVES AND MEDICINAL USE THEREOF

(57) The present invention provides glucopyranosyloxypyrazole derivatives represented by the general formula:



(I)

wherein one of Q and T represents a group represented by the general formula:



while the other represents a lower alkyl group or a halo (lower alkyl) group; $R^1$ represents a hydrogen atom, an optionally substituted lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, etc.; $R^2$ represents a hydrogen atom, an optionally substituted lower alkyl group, a lower alkoxy group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, etc., which exert an excellent inhibitory activity in human SGLT2, and therefore are useful as drugs for the prevention or treatment of a disease associated with hyper-

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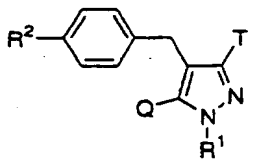
glycemia such as diabetes, diabetic complications or obesity, pharmaceutically acceptable salts thereof or prodrugs thereof, production intermediates thereof and pharmaceutical uses thereof.

## Description

### Technical Field

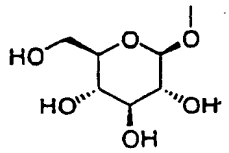
[0001] The present invention relates to glucopyranosyloxypyrazole derivatives, pharmaceutically acceptable salts thereof or prodrugs thereof which are useful as medicaments, production intermediates thereof and pharmaceutical uses thereof.

[0002] More particularly, the present invention relates to glucopyranosyloxypyrazole derivatives which have an inhibitory activity in human SGLT2, represented by the general formula:



(I)

wherein one of Q and T represents a group represented by the general formula:



while the other represents a lower alkyl group or a halo(lower alkyl) group; $R^1$ represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group or a group represented by the general formula: HO-$A^1$- wherein $A^1$ represents a lower alkylene group; $R^2$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and ahydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: HO-$A^2$- wherein $A^2$ represents a lower alkylene group; and with the proviso that $R^2$ does not represent either a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo( lower alkyl )group or a halogen atom when $R^1$ represents a hydrogen atom or a lower alkyl group, or pharmaceutically acceptable salts thereof and prodrugs thereof which are useful as agents for the prevention or treatment of a disease such as diabetes, diabetic complications or obesity.

### Background Art

[0003] Diabetes is one of lifestyle-related diseases with the background of change of eating habit and lack of exercise. Hence, diet and exercise therapies are performed in patients with diabetes. Furthermore, when its sufficient control and continuous performance are difficult, drug treatment is simultaneously performed. Now, biguanides, sulfonylureas and insulin sensitivity enhancers have been employed as antidiabetic agents. However, biguanides and sulfonylureas show occasionally adverse effects such as lactic acidosis and hypoglycemia, respectively. In a case of using insulin sensitivity enhancers, adverse effects such as edema are occasionally observed, and it is also concerned for advancing obesity. Therefore, in order to solve these problems, it has been desired to develop antidiabetic agents having a new mechanism.

[0004] In recent years, development of new type antidiabetic agents has been progressing, which promote urinary glucose excretion and lower blood glucose level by preventing excess glucose reabsorption at the kidney (J. Clin. Invest., Vol.79, pp.1510-1515 (1987)). In addition, it is reported that SGLT2 ($Na^+$/glucose cotransporter 2) is present in the S1 segment of the kidney's proximal tubule and participates mainly in reabsorption of glucose filtrated through glomerular (J. Clin. Invest., Vol.93, pp.397-404 (1994)). Accordingly, inhibiting a human SGLT2 activity prevents reabsorption of excess glucose at the kidney, subsequently promotes excreting excess glucose though the urine, and

normalizes blood glucose level. Therefore , fast development of antidiabetic agents, which have a potent inhibitory activity in human SGLT2 and have a new mechanism, has been desired. In addition, since such agents promote the excretion of excess glucose though the urine and consequently the glucose accumulation in the body is decreased, they are also expected to have a preventing or alleviating effect on obesity and a urinating effect. Furthermore , the agents are considered to be useful for various related diseases which occur accompanying the progress of diabetes or obesity due to hyperglycemia.

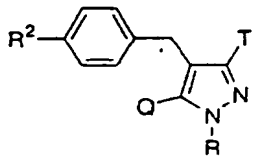
**[0005]** As compounds having pyrazole moiety, it is described that WAY-123783 increased an amount of excreted glucose in normal mice. However, its effects in human are not described at all (J. Med. Chem., Vol. 39, pp. 3920-3928 (1996)).

## Disclosure of the Invention

**[0006]** The present inventors have studied earnestly to find compounds having an inhibitory activity in human SGLT2. As a result, it was found that compounds represented by the above general formula (I) show an excellent inhibitory activity in human SGLT2, thereby forming the basis of the present invention.

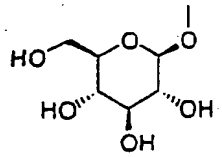
**[0007]** The present invention is to provide the following glucopyranosyloxypyrazole derivatives, pharmaceutically acceptable salts thereof and prodrugs thereof which exert an inhibitory activity in human SGLT2 and show an excellent hypoglycemic effect by excreting excess glucose in the urine through preventing the reabsorption of glucose at the kidney, and production intermediates thereof, and to provide pharmaceutical uses thereof.

**[0008]** This is, the present invention relates to a glucopyranosyloxypyrazole derivative represented by the general formula:




(I)

wherein one of Q and T represents a group represented by the general formula:




while the other represents a lower alkyl group or a halo(lower alkyl) group; $R^1$ represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group or a group represented by the general formula: HO-$A^1$- wherein $A^1$ represents a lower alkylene group; $R^2$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: HO-$A^2$- wherein $A^2$ represents a lower alkylene group; and with the proviso that $R^2$ does not represent either a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom when $R^1$ represents a hydrogen atom or a lower alkyl group, pharmaceutically acceptable salts thereof or prodrugs thereof.

**[0009]** Also, the present invention relates to a pharmaceutical composition, a human SGLT2 inhibitor and an agent for the prevention or treatment of a disease associated with hyperglycemia, which comprise as an active ingredient a glucopyranosyloxypyrazole derivative represented by the above general formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof.

**[0010]** The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of a glucopyranosyloxypyrazole derivative represented

by the above general formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof.

**[0011]** The present invention relates to a use of a glucopyranosyloxypyrazole derivative represented by the above general formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

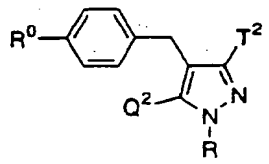
**[0012]** The present invention relates to a pharmaceutical combination which comprises (A) a glucopyranosyloxypyrazole derivative represented by the above general formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant,; a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-KB inhibitor, a lipid peroxidase inhibitor, an N-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a $\beta_3$-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an $\alpha_2$-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

**[0013]** The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of (A) a glucopyranosyloxypyrazole derivative represented by the above general formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof, in combination with (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist; a sodium channel antagonist, a transcript factor NF-KB inhibitor, a lipid peroxidase inhibitor, an N-acetylated-a-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a $\beta_3$-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative , a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an $\alpha_2$-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

**[0014]** The present invention relates to a use of (A) a glucopyranosyloxypyrazole derivative represented by the above general formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor,

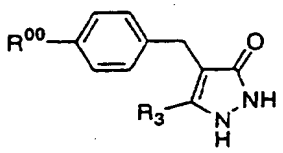
glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethylglutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a $\beta_3$-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an $\alpha_2$-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer, for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

**[0015]** Furthermore, the present invention relates to a glucopyranosyloxypyrazole derivative represented by the general formula:




(III)

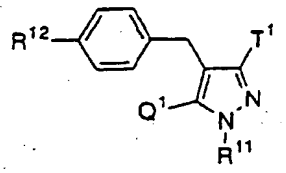
wherein one of $Q^2$ and $T^2$ represents 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy group and the other represents a lower alkyl group or a halo (lower alkyl) group; R represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, acyclic lower alkyl-substituted (lower alkyl) group or a group represented by the general formula: $P^{10}$-O-$A^1$- wherein $P^{10}$ represents a hydrogen atom or a hydroxy-protective group; and $A^1$ represents a lower alkylene group; $R^0$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo ( lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^{20}$-O-$A^2$- wherein $P^{20}$ represents a hydrogen atom or a hydroxy-protective group; and $A^2$ represents a lower alkylene group; and with the proviso that $R^0$ does not represent either a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo ( lower alkyl)group or a halogen atom when R represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof, and a glucopyranosyloxypyrazole derivative represented by the general formula:




(IVa)

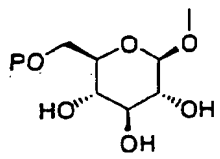
wherein $R^{00}$ represents a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^{20}$-O-$A^2$- wherein $P^{20}$ represents a hydrogen atom or a hydroxy-protective group; and $A^2$ represents a lower alkylene group; $R^3$ represents a lower alkyl group or a halo(lower alkyl) group, or a pharmaceutically acceptable salt thereof.

**[0016]** As prodrugs of the above mentioned glucopyranosyloxypyrazole derivatives, a compound represented by the general formula:



(II)

wherein one of $Q^1$ and $T^1$ represents a group represented by the general formula:



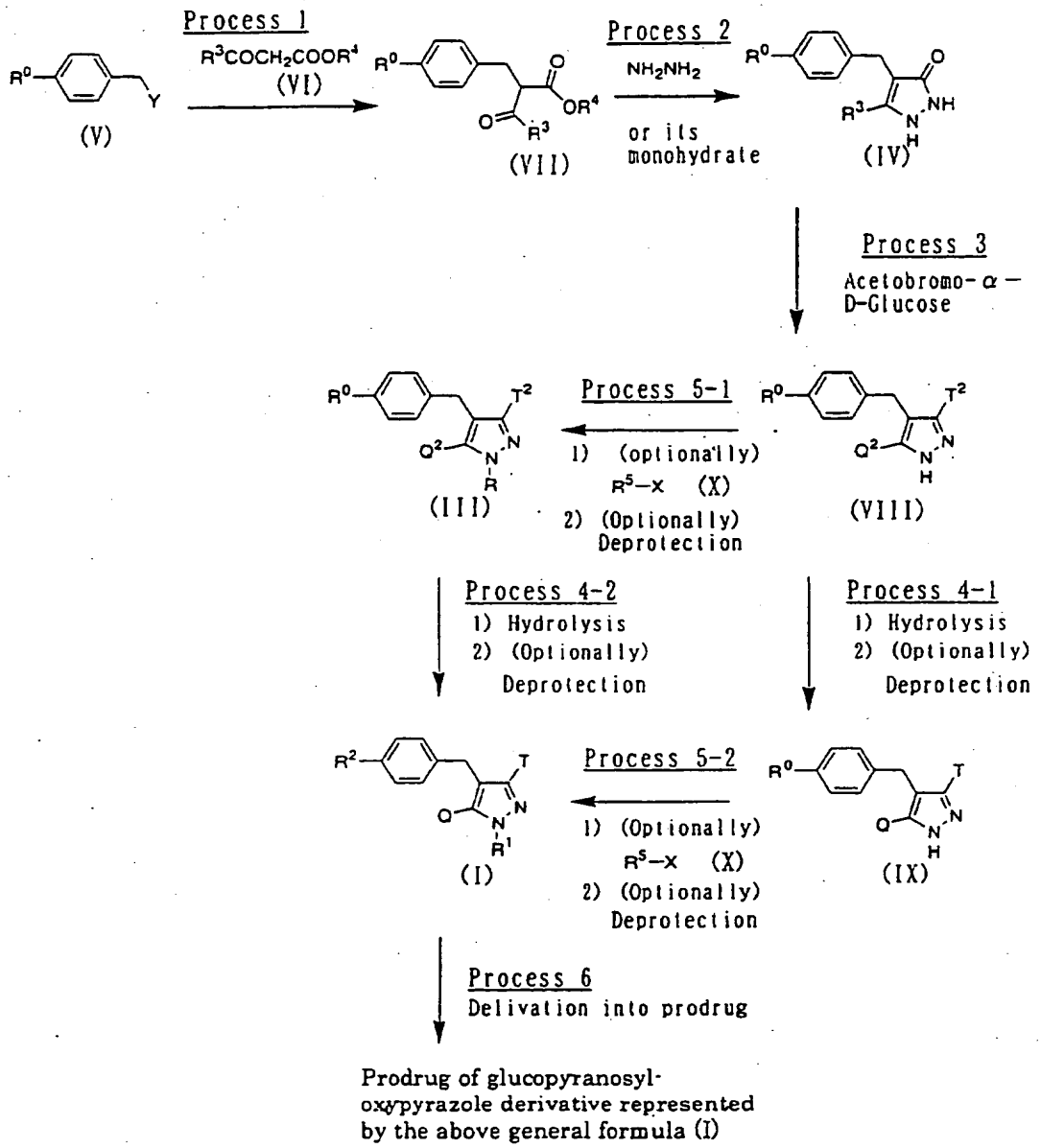
wherein P represents a hydrogen atom or a group forming prodrug; and the other represents a lower alkyl group or a halo(lower alkyl) group; $R^{11}$ represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group, a group forming prodrug or a group represented by the general formula: $P^1$-O-$A^1$- wherein $P^1$ represents a hydrogen atom or a group forming prodrug; and $A^1$ represents a lower alkylene group; $R^{12}$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkbxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^2$-O-$A^2$- wherein $P^2$ represents a hydrogen atom or a group forming prodrug; and $A^2$ represents a lower alkylene group; and with the proviso that $R^{12}$ does not represent either a hydrogen atom, a lower alkyl group , a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl)group or a halogen atom when at least one of P, $R^{11}$ and $R^{12}$ represents a group forming prodrug and $R^{11}$ represents a hydrogen atom or a lower alkyl group are illustrated.

**[0017]** In the present invention, the term "prodrug" means a compound which is converted into a glucopyranosyloxypyrazole derivative represented by the above general formula (I) as an active form thereof *in vivo*. As examples of groups forming prodrugs, in cases of such groups located at a hydroxy group, a hydroxy-protective group used generally as a prodrug such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group and a lower alkoxy-substituted (lower alkoxycarbonyl) group are illustrated, and in cases of such groups located at a nitrogen atom, an amino-protective group used generally as a prodrug such as a lower acyl group, a lower alkoxycarbonyl group, a lower acyloxymethyl group and a lower alkoxycarbonyloxymethyl group are illustrated.

**[0018]** In the present invention, the term "lower alkyl group" means a straight-chained or branched alkyl group having 1 to 6 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a tert-pentyl group, a hexyl group or the like; the term "lower alkoxy group" means a straight-chained or branched alkoxy group having 1 to 6 carbon atoms such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy group, an isopentyloxy group, aneopentyloxy group, a tert-pentyloxy group, a hexyloxy group or the like; and the term "lower alkylthio group" means a straight-chained or branched alkylthio group having 1 to 6 carbon atoms such as a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio group, a sec-butylthio group, a tert-butylthio group, a pentylthio group, an isopentylthio group, a neopentylthio group, a tert-pentylthio group, a hexylthio group or the like. The term "lower alkylene group" means a straight-chained or branched alkylene group having 1 to 6 carbon atoms such as a methylene group, an ethylene group, a trimethylene group, a propylene group or the like; the term "lower alkenyl group" means a straight-chained or branched alkenyl group having 2 to 6 carbon atoms such as a vinyl group, an allyl group, a 1-propenyl group, an isopropenyl group, a 1-butenyl group, a 2-butenyl group, a 2-methylallyl group, a 2-methyl-1-propenyl group or the like; the term "cyclic lower alkyl group" means a 3- to 7- member cyclic alkyl

group such as a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group or the like; the term "cyclic lower alkoxy group" means a 3- to 7-membered cyclic alkoxy group such as a cyclopropyloxy group, a cyclobutyloxy group, a cyclopentyloxy group, a cyclohexyloxy group, a cycloheptyloxy group or the like ; and the term "cyclic lower alkylidenemethyl group" means a 3-to 6-membered cyclic alkylidenemethyl group such as a cyclopropylidenemethyl group, a cyclobutylidenemethyl group, a cyclopentylidenemethyl group, a cyclohexylidenemethyl group or the like. The term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom; and the term "halo(lower alkyl) group" means the above lower alkyl group substituted by 1 to 3 different or same halogen atoms defined above. The term "lower acyl group" means a straight-chained, branched or cyclic acyl group having 2 to 7 carbon atoms such as an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a pivaloyl group, a hexanoyl group, a cyclohexylcarbonyl group or the like; and the term "lower alkoxy-substituted (lower acyl) group means the above lower acyl group substituted by the above lower alkoxy group. The term "lower alkoxycarbonyl group" means a straight-chained, branched or cyclic alkoxycarbonyl group having 2 to 7 carbon atoms such as a methoxycarbonyl group, an ethoxycarbonyl group, a propyloxycarbonyl group, an isopropyloxycarbonyl group, a butyloxycarbonyl group, an isobutyloxycarbonyl group, a sec-butyloxycarbonyl group, a tert-butyloxycarbonyl group, a pentyloxycarbonyl group, an isopentyloxycarbonyl group, a neo-pentyloxycarbonyl group, a tert-pentyloxycarbonyl group, a hexyloxycarbonyl group, and a cyclohexyloxycarbonyl group; the term "lower alkoxycarbonyl-substituted (lower acyl) group means the above lower acyl group substituted by the above lower alkoxycarbonyl group such as a 3-(ethoxycarbonyl)propionyl group; and the term "lower alkoxy-substituted (lower alkoxycarbonyl) group means the above lower alkoxycarbonyl group substituted by the above alkoxy group such as a 2-methoxyethoxycarbonyl group. The term "lower acyloxymethyl group" means a hydroxymethyl group *O*-substituted by the above lower acyl group; and the term "lower alkoxycarbonyloxymethyl group" means a hydroxymethyl group *O*-substituted by the above lower alkoxycarbonyl group. The term "5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring" means a univalent group derived from an aromatic heterocycle such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, pyrazole, imidazole, furazan, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine or the like. The term "hydroxy-protective group" means a hydroxy-protective group used in general organic synthesis such as a benzyl group, a methoxymethyl group, an acetyl group or the like.

**[0019]** The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention and prodrugs thereof can be prepared according to the following procedure:




wherein X and Y represent a leaving group such as a halogen atom, a mesyloxy group or a tosyloxy group; $R^3$ represents a lower alkyl group or a halo( lower alkyl) group; $R^4$ represents a methyl group or an ethyl group; $R^5$ represents a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group or a group represented by the general formula: $P^{10}$-O-$A^1$ - wherein $P^{10}$ and $A^1$ have the same meanings as defined above; and R, $R^0$, $R^1$, $R^2$, Q, $Q^2$, T and $T^2$ have the same meanings as defined above.

Process 1

**[0020]** A compound represented by the above general formula (VII) can be prepared by condensing a benzyl derivative represented by the above general formula (V) with a ketoacetate represented by the above general formula (VI) in the presence of a base such as sodium hydride or potassium *tert*-butoxide in an inert solvent. As the inert solvent

used in the reaction, 1,2-dimethoxyethane, tetrahydrofuran, *N,N*-dimethylformamide, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process 2

**[0021]** A benzylpyrazole derivative represented by the above general formula (IV) of the present invention can be prepared by condensing a compound represented by the above general formula (VII) with hydrazine or hydrazine monohydrate in an inert solvent. As the inert solvent used in the reaction, toluene, tetrahydrofuran, chloroform, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature. The obtained pyrazolone derivative represented by the above general formula (IV) can be also used in process 3 after converting into a salt thereof in a usual way.

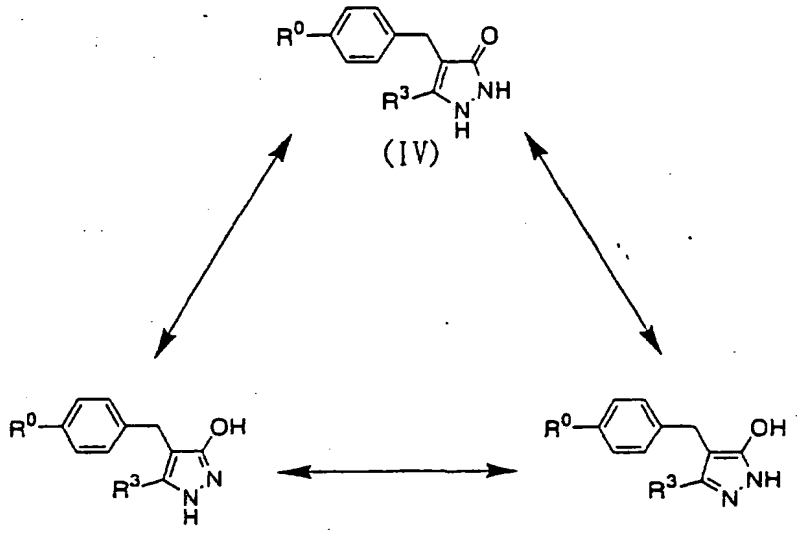
Process 3

**[0022]**

1) In case of benzylpyrazole derivatives represented by the above general formula (IV) wherein $R^3$ is a lower alkyl group, a corresponding compound represented by the above general formula (VIII) can be prepared by subjecting a corresponding benzylpyrazole derivative represented by the above general formula (IV) to glycosidation using acetobromo-α-D-glucose in the presence of abase such as silver carbonate in an inert solvent. As the solvent used in the glycosidation reaction, tetrahydrofuran and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

2) In case of benzylpyrazole derivatives represented by the above general formula (IV) wherein $R^3$ is a halo(lower alkyl) group, a corresponding compound represented by the above general formula (VIII) can be prepared by subjecting a corresponding benzylpyrazole derivative represented by the above general formula (IV) to glycosidation using acetobromo-α-D-glucose in the presence of a base such as potassium carbonate in an inert solvent. As the solvent used in the glycosidation reaction, acetonitrile, tetrahydrofuran and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

**[0023]** In the compounds represented by the above general formula (IV) of the present invention as starting materials, there can be the following three tautomers, varying based on the change of reaction conditions. The compounds represented by the above general formula (IV) of the present invention include all compounds described as the following states:




wherein $R^0$ and $R^3$ have the same meanings as defined above.

Process 4-1

**[0024]** A glucopyranosyloxypyrazole derivative represented by the above general formula (IX) can be prepared by subjecting a compound represented by the above general formula (VIII) to alkaline hydrolysis and optionally removal of a hydroxy-protective group in a usual way. As the solvent used in the alkaline hydrolysis , methanol, ethanol, tetrahydrofuran, water, a mixed solvent thereof and the like can be illustrated, and as the base used, sodium hydroxide, sodium methoxide, sodium ethoxide and the' like can be illustrated. The reaction temperature is usually from 0°C to room temperature, and the reaction time is usually from 30 minutes to 6 hours, varying based on a used starting material, solvent and reaction temperature.

Process 4-2

**[0025]** A glucopyranosyloxypyrazole derivative represented by the above general formula (I) of the present invention can be prepared by subjecting a compound represented by the above general formula (III) to alkaline hydrolysis and optionally removal of a hydroxy-protective group in a usual way. As the solvent used in the hydrolysis reaction, methanol, ethanol, tetrahydrofuran, water, a mixed solvent thereof and the like can be illustrated, and as the base, sodium hydroxide, sodium methoxide, sodium ethoxide and the like can be illustrated. The reaction temperature is usually from 0°C to room temperature, and the reaction time is usually from 30 minutes to 6 hours, varying based on a used starting material, solvent and reaction temperature.

Process 5-1

**[0026]** A compound represented by the above general formula (III) of the present invention can be prepared by subjecting a glucopyranosyloxypyrazole derivative represented by the above general formula (VIII) to *N*-alkylation optionally using an *N*-alkylating agent represented by the above general formula (X) in the presence of a base such as potassium carbonate or cesium carbonate in an inert solvent, and optionally to deprotection in a usual way. As the inert solvent used in the *N*-alkylation, acetonitrile, *N,N*-dimethylformamide, tetrahydrofuran, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature. The obtained compound represented by the above general formula (III) can be also used in process 4-2 after converting into a salt thereof in a usual way.

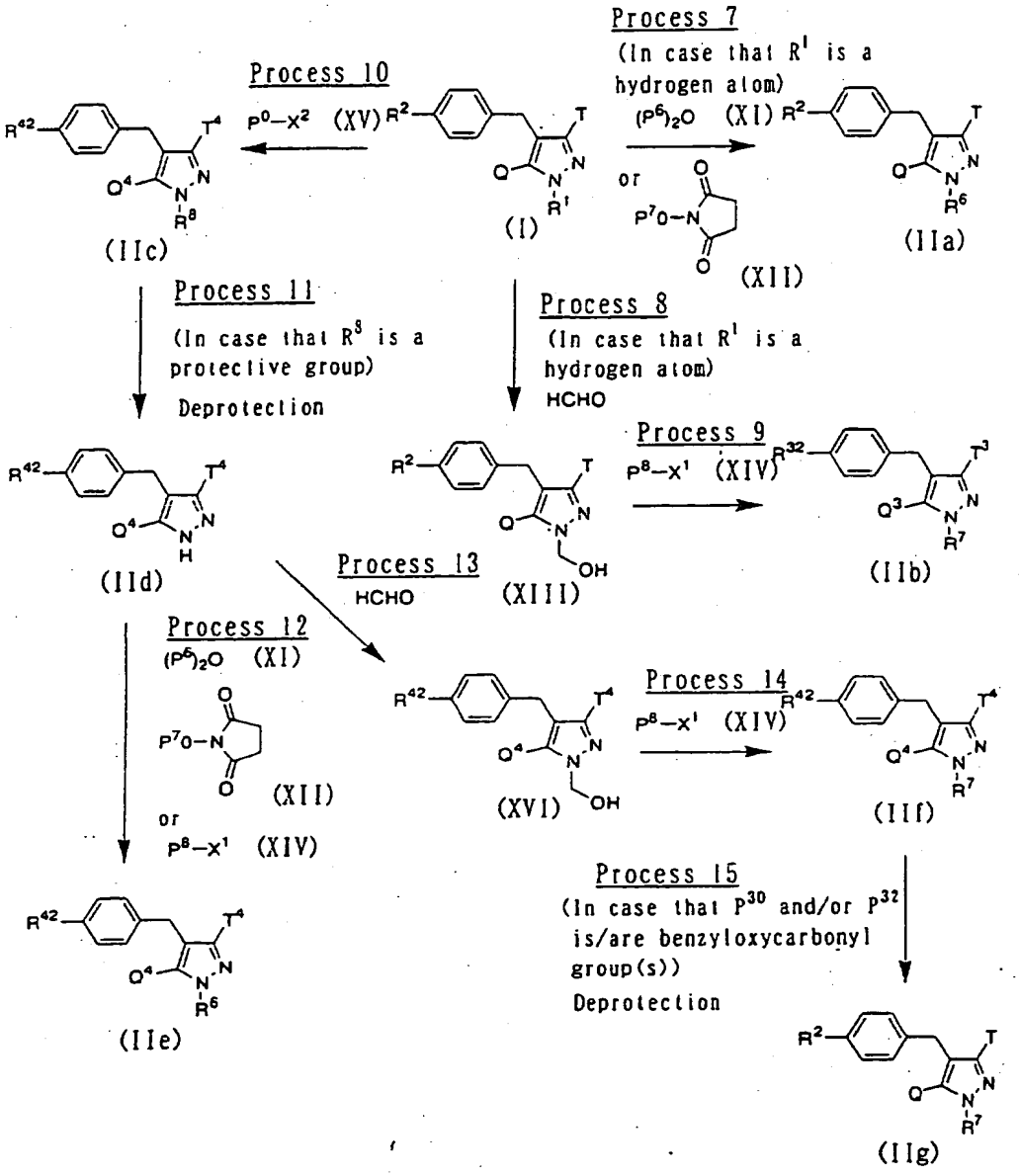
Process 5-2

**[0027]** A compound represented by the above general formula (I) of the present invention can be prepared by subjecting a glucopyranosyloxypyrazole derivative represented by the above general formula (IX) to *N*-alkylation optionally using an *N*-alkylating agent represented by the above general formula (X) in the presence of a base such as potassium carbonate or cesium carbonate, and occasionally a catalytic amount of sodium iodide in an inert solvent, and optionally to deprotection in a usual way. As the inert solvent used in the *N*-alkylation, *N,N*-dimethylformamide, 1,2-dimethoxyethane, dimethyl sulfoxide, tetrahydrofuran, ethanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process 6

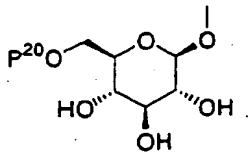
**[0028]** A prodrug of a glucopyranosyloxypyrazole derivative represented by the above general formula (I) (including a prodrug represented by the above general formula (II)) can be prepared by introducing hydroxy- and/or amino-protective groups generally capable for use in a prodrug into a hydroxy group and/or a nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) in a usual way.

**[0029]** For example, the derivation reaction to a prodrug in the above process 6 can be done according to the following procedure or analogous procedures thereof:

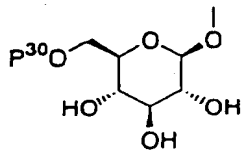



wherein $P^0$ represents a hydroxy-protective group such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group, a lower alkoxy-substituted (lower alkoxycarbonyl) group or a benzyloxycarbonyl group; $P^6$ represents a lower acyl group; $P^7$ represents a lower alkoxycarbonyl group; $P^8$ represents a lower acyl group or a lower alkoxycarbonyl group; $R^6$ represents a lower acyl group or a lower alkoxycarbonyl group; $R^7$ represents a lower acyloxymethyl group or a lower alkoxycarbonyloxymethyl group; $R^8$ represents a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group, a lower alkoxy-substituted (lower alkoxycarbonyl) group, a benzyloxycarbonyl group, or a group represented by the general formula: $P^{21}$-O-$A^1$- wherein $P^{21}$ represents a hydrogen atom or a hydroxy-protective group such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group, a lower alkoxy-substituted (lower alkoxycarbonyl) group or a benzyloxycarbonyl group; and $A^1$ represents a lower alkylene group; $X^1$ and $X^2$ represent a

leaving group such as a bromine atom or a chlorine atom; one of $Q^3$ and $T^3$ represents a group represented by the general formula:



wherein $P^{20}$ represents a hydrogen atom, a lower acyl group or a lower alkoxycarbonyl group; and the other represents a lower alkyl group orahalo(lower alkyl) group; $R^{32}$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo( lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, or a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a5-or 6 -membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^{22}$-O-$A^2$- wherein $P^{22}$ represents a hydrogen atom, a lower acyl group or a lower alkoxycarbonyl group; and $A^2$ represents a lower alkylene group; and with the proviso that at least one of $P^{20}$ and $P^{22}$ represents a lower acyl group or a lower alkoxycarbonyl group and one of $Q^4$ and $T^4$ represents a group represented by the general formula:



wherein $P^{30}$ represents a hydrogen atom or a hydroxy-protective group such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group, a lower alkoxy-substituted (lower alkoxycarbonyl) group or a benzyloxycarbonyl group; and the other represents a lower alkyl group or a halo(lower alkyl) group; $R^{42}$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, or a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group. a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^{32}$-O-$A^2$- wherein $P^{32}$ represents a hydrogen atom or a hydroxy-protective group such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group, a lower alkoxy-substituted (lower alkoxycarbonyl) group or a benzyloxycarbonyl group; and $A^2$ represents a lower alkylene group; and with the proviso that at least one of $P^{21}$, $P^{30}$ and $P^{32}$ represents a hydroxy-protective group such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group, a lower alkoxy-substituted (lower alkoxycarbonyl). group or a benzyloxycarbonyl group; and $R^1$, $R^2$, Q and T have the same meanings as defined above.

Process 7

**[0030]** A prodrug represented by the above general formula (IIa) can be prepared by protecting a nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (I) with an aliphatic acid anhydride represented by the above general formula (XI) in an aliphatic acid such as acetic acid at usually 0°C to reflux temperature for usually 30 minutes to 1 day, or alternatively, with a succinimide derivative represented by the above general formula (XII) in an inert solvent such as tetrahydrofuran at usually room temperature to reflux temperature for 1 hour to 1 day. The reaction time can be appropriately varied based on a used starting material, solvent and reaction temperature.

Process 8

**[0031]** A compound represented by the above general formula (XIII) can be prepared by introducing a hydroxymethyl group into a nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (I) using formaldehyde in a various solvent. As the solvent used in the reaction, water, methanol, ethanol, tetrahydrofuran, dichloromethane, ethyl acetate, *N,N*-dimethylformamide, acetonitrile, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process 9

**[0032]** A prodrug represented by the above general formula (IIb) can be prepared by protecting the hydroxymethyl group of a compound represented by the above general formula (XIII) with a reagent for protection represented by the above general formula (XIV) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1, 2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on a used starting material, solvent and reaction temperature.

Process 10

**[0033]** A prodrug represented by the above general formula (IIc) or an analogous compound thereof can be prepared by protecting a nitrogen atom and/or a hydroxy group of a glucopyranosyloxypyrazole derivative represented by the above general formula (I) with a reagent for protection represented by the above general formula (XV) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]-octane in an inert solvent or without any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on a used starting material, solvent and reaction temperature.

Process 11

**[0034]** A prodrug represented by the above general formula (IId) or an analogous compound thereof can be prepared by subjecting a compound represented by the above general formula (IIc) to deacylation in the presence of a weak base such as sodium hydrogen carbonate, sodium carbonate or potassium carbonate in an alcoholic solvent such as methanol or ethanol. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 15 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process 12

**[0035]** A prodrug represented by the above general formula (IIe) or an analogous compound thereof can be prepared by protecting a nitrogen atom of a compound represented by the above general formula (IId) with an aliphatic acid anhydride represented by the above general formula (XI) in an aliphatic acid such as acetic acid at usually 0°C to reflux temperature for usually 30 minutes to 1 day, or alternatively, with a succinimide derivative represented by the above general formula (XII) in an inert solvent such as tetrahydrofuran at usually room temperature to reflux temperature for 1 hour to 1 day, and further alternatively, with a reagent for protection represented by the above general formula (XIV) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent such as dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, tert-butanol or a mixed solvent thereof, or without any solvent at usually -40°C to reflux temperature for 30 minutes to 2 days. The reaction time can be appropriately varied based on a used starting material, solvent and reaction temperature.

Process 13

**[0036]** A compound represented by the above general formula (XVI) can be prepared by introducing a hydroxymethyl group into a nitrogen atom of a compound represented by the above general formula (IId) using formaldehyde in a various solvent. As the solvent used in the reaction, water, methanol, ethanol, tetrahydrofuran, dichloromethane, ethyl acetate, *N,N*-dimethylformamide, acetonitrile, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

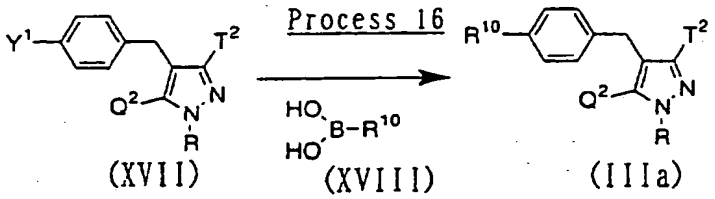
Process 14

**[0037]** A prodrug represented by the above general formula (IIf) or an analogous compound thereof can be prepared by protecting a hydroxymethyl group of a compound represented by the above general formula (XVI) with a reagent for protection represented by the above general formula (XIV) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, tert-butanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on a used starting material, solvent and reaction temperature.

Process 15

**[0038]** A prodrug represented by the above general formula (IIg) can be prepared by subjecting a compound represented by the above general formula (IIf) to deprotection in the presence of a palladium catalyst such as palladium carbon powder in an inert solvent. As the inert solvent used in the reaction, methanol, ethanol, tetrahydrofuran, ethyl acetate, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material., solvent and reaction temperature.

**[0039]** Of the compounds represented by the above general formula (III), the following compounds wherein $R^0$ is a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, or a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring can also be prepared according to the following procedure:




(XVII) (XVIII) (IIIa)

wherein $R^{10}$ represents a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, or a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring; $Y^1$ represents a leaving group such as a chlorine atom, a bromine atom or an iodine atom; and R, $Q^2$ and $T^2$ have the same meanings as defined above.

Process 16

**[0040]** A compound represented by the above general formula (IIIa) can be prepared by subjecting a glucopyranosyloxypyrazole derivative represented by the above general formula (XVII) that can be prepared using a corresponding starting material in a similar way to the above processes 1 to 3 and 5-1 to Suzuki coupling reaction using a borate compound represented by the above general formula (XVIII) in the presence of a base such as cesium fluoride, sodium carbonate, potassium carbonate, and potassium *tert*-butoxide, and metal catalyst such as tetrakis(triphenylphosphine) palladium(0), bis(dibenzylidene acetone)palladium(0), bis(triphenylphosphine)palladium(II) dichloride in a various solvent. As the solvent used in the reaction, 1,2-dimethoxyethane, toluene, ethanol, water, amixed solvent thereof and

the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

**[0041]** The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) and the prodrugs thereof of the present invention obtained by the above production processes can be isolated and purified by conventional separation means such as fractional recrystallization, purification using chromatography, solvent extraction and solid phase extraction. Procedures for isolation or purification can be performed occasionally in any production process of glucopyranosyloxypyrazole derivatives represented by the above general formula (I) and prodrugs thereof.

**[0042]** The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention and prodrugs thereof can be converted into their pharmaceutically acceptable salts in a usual way. Examples of such salts include acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the'like, acid addition salts with organic acids such as formic acid, acetic acid, adipic acid, citric acid, fumaric acid, maleic acid, oleic acid, lactic acid, stearic acid, succinic acid, tartaric acid, propionic acid, butyric acid, oxalic acid, malonic acid, malic acid, carbonic acid, glutamic acid, aspartic acid, methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid and the like, salts with organic amines such as 2-aminoethanol, piperidine, morpholine , pyrrolidine and the like, and salts with inorganic bases such as a sodium salt, a potassium salt, a calcium salt, a magnesium salt and the like.

**[0043]** The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention and prodrugs thereof include their solvates with pharmaceutically acceptable solvents such as ethanol and water.

**[0044]** Among the glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention and prodrugs thereof, there are two geometrical isomers in each compound having unsaturated bond. In the present invention, either of cis(*Z*)-isomer or trans(*E*)-isomer can be employed.

**[0045]** Among the glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention and prodrugs thereof, there are two optical isomers, *R*-isomer and *S*-isomer, in each compound having an asymmetric carbon atom excluding the glucopyranosyloxy moiety. In the present invention, either of *R*-isomer or *S*-isomer can be employed, and a mixture of both isomers can be also employed.

**[0046]** The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention and prodrugs thereof show an excellent inhibitory activity in human SGLT2. On the other hand, since WAY-123783 has an extremely weak inhibitory activity in human SGLT2, it can not be expected that it exerts an enough effect as a human SGLT2 inhibitor. Therefore, the glucopyranosyloxypyrazole derivatives represented of the present invention and prodrugs thereof are extremely useful as drugs for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications (e.g., retinopathy, neuropathy, nephropathy, ulcer, macroangiopathy), obesity, hyperinsulinemia, glucosemetabolismdisorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia, gout or the like.

**[0047]** Furthermore, the compounds of the present invention can be suitably used in combination with at least one member selected from drugs other than SGLT2 inhibitors. Examples of the drugs which can be used in combination with the compounds of the present invention include an insulin sensitivity enhancer, a glucose absorption inhibitor a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue , an amylin agonist, analdose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an N-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor (PDGF), a platelet-derived growth factor (PDGF) analogue (e.g., PDGF-AA, PDGF-BB, PDGF-AB), epidermal growth factor (EGF), nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a $\beta_3$-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyltransferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an $\alpha_2$-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

**[0048]** In case of uses of the compound of the present invention in combination with the above one or more drugs, the present invention includes either dosage forms of simultaneous administration as a single preparation or separated preparations in way of same or different administration route, and administration at different dosage intervals as separated preparations in way of same or different administration route. A pharmaceutical combination comprising the compound of the present invention and the above one or more drugs includes both dosage forms as a single preparation and separated preparations for combination as mentioned above.

**[0049]** The compounds of the present invention can obtain more advantageous effects than additive effects in the prevention or treatment of the above diseases when using suitably in combination with the above drugs. Also, the administration dose can be decreased in comparison with administration of either drug alone, or adverse effects of coadministrated drugs other than SGLT2 inhibitors can be avoided or declined.

**[0050]** Concrete compounds as the above drugs used for combination and preferable diseases to be treated are exemplified as follows . However, the present invention is not limited thereto, and for example, the concrete compounds include their free compounds, and their or other pharmaceutically acceptable salts.

**[0051]** As insulin sensitivity enhancers, peroxisome proliferator-activated receptor-γ agonists such as troglitazone, pioglitazone hydrochloride, rosiglitazone maleate, sodium darglitazone, GI-262570, isaglitazone, LG-100641, NC-2100, T-174, DRF-2189, CLX-0921, CS-011, GW-1929, ciglitazone, sodium englitazone and NIP-221, peroxisome proliferator-activated receptor-α agonists such as GW-9578 and BM-170744, peroxisome proliferator-activatedreceptor-a/γ agonists such as GW-409544, KRP-297, NN-622, CLX-0940, LR-90, SB-219994, DRF-4158 and DRF-MDX8 , retinoidXreceptor agonists such as ALRT-268, AGN-4204 , MX-6054, AGN-194204, LG-100754 and bexarotene, and other insulin sensitivity enhancers such as reglixane, ONO-5816, MBX-102, CRE-1625, FK-614, CLX-0901, CRE-1633, NN-2344, BM-13125, BM-501050, HQL-975, CLX-0900, MBX-668, MBX-675, S-15261, GW-544, AZ-242, LY-510929, AR-H049020 and GW-501516 are illustrated. Insulin sensitivity enhancers are used preferably for diabetes, diabetic complications, obesity, hyperinsulinemia, glucose metabolism disorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for diabetes, hyperinsulinemia or glucose metabolism disorder because of improving the disturbance of insulin signal transduction in peripheral tissues and enhancing glucose uptake into the tissues from the blood, leading to lowering blood glucose level.

**[0052]** As glucose absorption inhibitors, α-glucosidase inhibitors such as acarbose, voglibose, miglitol, CKD-711, emiglitate, MDL-25,637, camiglibose and MDL-73,945, and α-amylase inhibitors such as AZM-127 are illustrated. Glucose absorption inhibitors are used preferably for diabetes, diabetic complications, obesity, hyperinsulinemia or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder because of inhibiting the gastrointestinal enzymatic digestion of carbohydrates contained in foods, and inhibiting or delaying the absorption of glucose into the body.

**[0053]** As biguanides, phenformin, buformin hydrochloride, metformin hydrochloride and the like are illustrated. Biguanides are used preferably for diabetes, diabetic complications, hyperinsulinemia or glucose metabolism disorder, and more preferably for diabetes, hyperinsulinemia or glucose metabolism disorder because of lowering blood glucose level by inhibitory effects on hepatic gluconeogenesis, accelerating effects on anaerobic glycolysis in tissues or improving effects on insulin resistance in peripheral tissues.

**[0054]** As insulin secretion enhancers, tolbutamide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glyburide (glibenclamide), gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibornuride, glipizide, gliquidone, glisoxapide, glybuthiazol, glybuzole, glyhexamide, sodium glymidine, glypinamide, phenbutamide, tolcyclamide, glimepiride, nateglinide, mitiglinide calcium hydrate, repaglinide and the like are illustrated. Insulin secretion enhancers are used preferably for diabetes, diabetic complications or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder because of lowering blood glucose level by acting on pancreatic β-cells and enhancing the insulin secretion.

**[0055]** As insulin preparations, human insulin, human insulin analogues, animal-deprived insulin and the like are illustrated. Insulin preparations are used preferably for diabetes, diabetic complications or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder.

**[0056]** As glucagon receptor antagonists, BAY-27-9955, NNC-92-1687 and the like are illustrated; as insulin receptor kinase stimulants, TER-17411, L-783281, KRX-613 and the like are illustrated; as tripeptidyl peptidase II inhibitors, UCL-1397 and the like are illustrated; as dipeptidyl peptidase IV inhibitors, NVP-DPP728A, TSL-225, P-32/98 and the like are illustrated; as protein tyrosine phosphatase 1B inhibitors, PTP-112, OC-86839, PNU-177496 and the like are illustrated; as glycogen phosphorylase inhibitors, NN-4201, CP-368296 and the like are illustrated; as fructose-bisphosphatase inhibitors, R-132917 and the like are illustrated; as pyruvate dehydrogenase inhibitors, AZD-7545 and the like are illustrated; as hepatic gluconeogenesis inhibitors, FR-225659 and the like are illustrated; as glucagon-like peptide-1 analogues, exendin-4, CJC-1131 and the like are illustrated; as glucagon-like peptide 1 agonists; AZM-134, LY-315902 and the like are illustrated; and as amylin, amylin analogues or amylin agonists, pramlintide acetate and the like are illustrated. These drugs, glucose-6-phosphatase inhibitors, D-chiroinsitol, glycogen synthase kinase-3 inhibitors, glucagon-like peptide-1 are used preferably for diabetes, diabetic complications, hyperinsulinemia or glucose

metabolism disorder, and more preferably for diabetes or glucose metabolism disorder.

**[0057]** As aldose reductase inhibitors, ascorbyl gamolenate, tolrestat, epalrestat, ADN-138, BAL-ARI8, ZD-5522, ADN-311, GP-1447, IDD-598, fidarestat, sorbinil, ponalrestat, risarestat, zenarestat, minalrestat, methosorbinil, AL-1567, imirestat, M-16209, TAT, AD-5467, zopolrestat, AS-3201,NZ-314, SG-210, JTT-811, lindolrestat and the like are illustrated. Aldose reductase inhibitors are preferably used for diabetic complications because of inhibiting aldose reductase and lowering excessive intracellular accumulation of sorbitol in accelerated polyol pathway which are in continuous hyperglycemic condition in the tissues in diabetic complications.

**[0058]** As advanced glycation endproducts formation inhibitors, pyridoxamine, OPB-9195, ALT-946, ALT-711, pimagedine hydrochloride and the like are illustrated. Advanced glycation endproducts formation inhibitors are preferably used for diabetic complications because of inhibiting formation of advanced glycation endproducts which are accelerated in continuous hyperglycemic condition in diabetes and declining cellular damage.

**[0059]** As protein kinase C inhibitors, LY-333531, midostaurin and the like are illustrated. Protein kinase C inhibitors are preferably used for diabetic complications because of inhibiting protein kinase C activity which is accelerated in continuous hyperglycemic condition in diabetes.

**[0060]** As γ-aminobutyric acid receptor antagonists, topiramate and the like are illustrated; as sodium channel antagonists, mexiletine hydrochloride, oxcarbazepine and the like are illustrated; as transcrit factor NF-κB inhibitors, dexlipotam and the like are illustrated; as lipid peroxidase inhibitors, tirilazad mesylate and the like are illustrated; as N-acetylated-α-linked-acid-dipeptidase inhibitors, GPI-5693 and the like are illustrated; and as carnitine derivatives, carnitine, levacecarnine hydrochloride, levocarnitine chloride, levocarnitine, ST-261 and the like are illustrated. These drugs, insulin-like growth factor-I, platelet-derived growth factor, platelet derived growth factor analogues, epidermal growth factor, nerve growth factor, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide and Y-128 are preferably used for diabetic complications.

**[0061]** As hydroxymethylglutaryl coenzyme A reductase inhibitors, sodium cerivastatin, sodium pravastatin, lovastatin, simvastatin, sodium fluvastatin, atorvastatin calcium hydrate, SC-45355, SQ-33600, CP-83101, BB-476, L-669262, S-2468, DMP-565, U-20685, BAY-x-2678, BAY-10-2987, calcium pitavastatin, calcium rosuvastatin, colestolone, dalvastatin, acitemate, mevastatin, crilvastatin, BMS-180431, BMY-21950, glenvastatin, carvastatin, BMY-22089, bervastatin and the like are illustrated. Hydroxymethylglutaryl coenzyme A reductase inhibitors are used preferably for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for hyperlipidemia, hypercholesterolemia or atherosclerosis because of lowering blood cholesterol level by inhibiting hydroxymethylglutaryl coenzyme A reductase.

**[0062]** As fibric acid derivatives, bezafibrate, beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, aluminum clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, AHL-157 and the like are illustrated. Fibric acid derivatives are used preferably for hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for hyperlipidemia, hypertriglyceridemia or atherosclerosis because of activating hepatic lipoprotein lipase and enhancing fatty acid oxidation, leading to lowering blood triglyceride level.

**[0063]** As $\beta_3$-adrenoceptor agonists, BRL-28410, SR-58611A, ICI-198157, ZD-2079, BMS-194449, BRL-37344, CP-331679, CP-114271, L-750355, BMS-187413, SR-59062A, BMS-210285, LY-377604, SWR-0342SA, AZ-40140, SB-226552, D-7114, BRL-35135, FR-149175, BRL-26830A, CL-316243, AJ-9677, GW-427353, N-5984, GW-2696 and the like are illustrated. $\beta_3$-Adrenoceptor agonists are used preferably for obesity, hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder, and more preferably for obesity or hyperinsulinemia because of stimulating $\beta_3$-adrenoceptor in adipose tissue and enhancing the fatty acid oxidation, leading to induction of energy expenditure.

**[0064]** As acyl-coenzyme A cholesterol acyltransferase inhibitors, NTE-122, MCC-147, PD-132301-2, DUP-129, U-73482, U-76807, RP-70676, P-06139, CP-113818, RP-73163, FR-129169, FY-038, EAB-309, KY-455, LS-3115, FR-145237, T-2591, J-104127, R-755, FCE-28654, YIC-C8-434, avasimibe, CI-976, RP-64477, F-1394, eldacimibe, CS-505, CL-283546, YM-17E, lecimibide, 447C88, YM-750, E-5324, KW-3033, HL-004, eflucimibe and the like are illustrated. Acyl-coenzyme A cholesterol acyltransferase inhibitors are used preferably for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder, and more preferably for hyperlipidemia or hypercholesterolemia because of lowering blood cholesterol level by inhibiting acyl-coenzyme A cholesterol acyltransferase.

**[0065]** As thyroid hormone receptor agonists, sodium liothyronine, sodium levothyroxine, KB-2611 and the like are illustrated; as cholesterol absorption inhibitors, ezetimibe, SCH-48461 and the like are illustrated; as lipase inhibitors, orlistat, ATL-962, AZM-131, RED-103004 and the like are illustrated; as carnitine palmitoyltransferase inhibitors, etomoxir and the like are illustrated; as squalene synthase inhibitors, SDZ-268-198, BMS-188494, A-87049, RPR-101821, ZD-9720, RPR-107393, ER-27856 and the like are illustrated; as nicotinic acid derivatives, nicotinic acid, nicotinamide, nicomol, niceritrol, acipimox, nicorandil and the like are illustrated; as bile acid sequestrants, colestyramine, colestilan, colesevelam hydrochloride, GT-102-279 and the like are illustrated; as sodium/bile acid cotransporter inhibitors, 264W94, S-8921, SD-5613 and the like are illustrated; and as cholesterol ester transfer protein inhibitors, PNU-

107368E, SC-795, JTT-705, CP-529414 and the like are illustrated. These drugs, probcol, microsomal triglyceride transfer protein inhibitors, lipoxygenase inhibitors and low-density lipoprotein receptor enhancers are preferably used for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder.

**[0066]** As appetite suppressants, monoamine reuptake inhibitors, serotonin reuptake inhibitors, serotonin releasing stimulants, serotonin agonists (especially $5HT_{2c}$-agonists), noradrenalin reuptake inhibitors, noradrenalin releasing stimulants, $\alpha_1$-adrenoceptor agonists, $\beta_2$-adrenoceptor agonists, dopamine agonists, cannabinoidreceptor antagonists,γ-aminobutyric acid receptor antagonists, $H_3$-histamine antagonists, L-histidine, leptin, leptin analogues, leptin receptor agonists, melanocortin receptor agonists (especially, MC3-R agonists, MC4-R agonists), α-melanocyte stimulating hormone, cocaine-and amphetamine-regulated transcript, mahogany protein, enterostatin agonists, calcitonin, calcitonin-gene-related peptide, bombesin, cholecystokinin agonists (especially CCK-A agonists), corticotropin-releasing hormone, corticotrophin-releasing hormone analogues, corticotropin-releasing hormone agonists, urocortin, somatostatin, somatostatin analogues, somatostatin receptor agonists, pituitary adenylate cyclase-activating peptide, brain-derived neurotrophic factor, ciliary neurotrophic factor, thyrotropin-releasing hormone, neurotensin, sauvagine, neuropeptide Y antagonists, opioid peptide antagonists, galanin antagonists, melanin-concentrating hormone'antagonists, agouti-related protein inhibitors and orexin receptor antagonists are illustrated. Concretely, as monoamine reuptake inhibitors, mazindol and the like are illustrated; as serotonin reuptake inhibitors, dexfenfluramine hydrochloride, fenfluramine, sibutramine hydrochloride, fluvoxamine maleate, sertraline hydrochloride and the like are illustrated; as serotonin agonists, inotriptan, (+)-norfenfluramine and the like are illustrated; as noradrenaline reuptake inhibitors, bupropion, GW-320659 and the like are illustrated; as noradrenaline releasing stimulants, rolipram, YM-992 and the like are illustrated; as $\beta_2$-adrenoceptor agonists, amphetamine, dextroamphetamine, phentermine, benzphetamine, methamphetamine, phendimetrazine, phenmetrazine, diethylpropion, phenylpropanolamine, clobenzorex and the like are illustrated; as dopamine agonists, ER-230, doprexin, bromocriptine mesylate and the like are illustrated; as cannabinoid receptor antagonists, rimonabant and the like are illustrated; as γ-aminobutyric acid receptor antagonists, topiramate and the like are illustrated; as $H_3$-histamine antagonists, GT-2394 and the like are illustrated; as leptin, leptin analogues or leptin receptor agonists, LY-355101 and the like are illustrated; as cholecystokinin agonists (especially CCK-A agonists), SR-146131, SSR-125180, BP-3.200, A-71623, FPL-15849, GI-248573, GW-7178, GI-181771, GW-7854, A-71378 and the like are illustrated; and as neuropeptide Y antagonists, SR-120819-A, PD-160170, NGD-95-1, BIBP-3226, 1229-U-91, CGP-71683, BIBO-3304, CP-671906-01, J-115814 and the like are illustrated. Appetite suppressants are used preferably for diabetes, diabetic complications, obesity, glucose metabolism disorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia or gout, and more preferably for obesity because of stimulating or inhibiting the activities of intracerebral monoamines or bioactive peptides in central appetite regulatory system and suppressing the appetite, leading to reduction of energy intake.

**[0067]** As angiotensin-converting enzyme inhibitors, captopril, enalapri maleate, alacepril, delapril hydrochloride, ramipril, lisinopril, imidaprilhydrochloride, benazeprilhydrochloride, ceronapril monohydrate, cilazapril, sodium fosinopril, perindopril erbumine, calcium moveltipril, quinapril hydrochloride, spirapril hydrochloride, temocapril hydrochloride, trandolapril, calcium zofenopril, moexipril hydrochloride, rentiapril and the like are illustrated. Angiotensin-converting enzyme inhibitors are preferably used for diabetic complications or hypertension.

**[0068]** As neutral endopeptidase inhibitors, omapatrilat, MDL-100240, fasidotril, sampatrilat, GW-660511X, mixanpril, SA-7060, E-4030, SLV-306, ecadotril and the like are illustrated. Neutral endopeptidase inhibitors are preferably used for diabetic complications or hypertension.

**[0069]** As angiotensin II receptor antagonists, candesartan cilexetil, candesartan cilexetil/hydrochlorothiazide, potassium losartan, eprosartan mesylate, valsartan, telmisartan, irbesartan, EXP-3174, L-158809, EXP-3312, olmesartan, tasosartan, KT-3-671, GA-0113, RU-64276, EMD-90423, BR-9701 and the like are illustrated. Angiotensin II receptor antagonists are preferably used for diabetic complications or hypertension.

**[0070]** As endothelin-converting enzyme inhibitors, CGS-31447, CGS-35066, SM-19712 and the like are illustrated; as endothelin receptor antagonists, L-749805, TBC-3214, BMS-182874, BQ-610, TA-0201, SB-215355, PD-180988, sodium sitaxsentan, BMS-193884, darusentan, TBC-3711, bosentan, sodium tezosentan, J-104132, YM-598, S-0139, SB-234551, RPR-118031A, ATZ-1993, RO-61-1790, ABT-546, enlasentan, BMS-207940 and the like are illustrated. These drugs are preferably used for diabetic complications or hypertension, and more preferably for hypertension.

**[0071]** As diuretic agents, chlorthalidone, metolazone, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, methyclothiazide, indapamide, tripamide, mefruside, azosemide, etacrynic acid, torasemide, piretanide, furosemide, bumetanide, meticrane, potassium canrenoate, spironolactone, triamterene, aminophylline, cicletanine hydrochloride, LLU-α, PNU-80873A, isosorbide, D-mannitol, D-sorbitol, fructose, glycerin, acetazolamide, methazolamide, FR-179544, OPC-31260, lixivaptan, conivaptan hydrochloride and the like are illustrated. Diuretic drugs are preferably used for diabetic complications, hypertension, congestive heart failure or edema, and more preferably for hypertension, congestive heart failure or edema because of reducing blood pressure or improving edema by increasing urinary excretion.

[0072] As calcium antagonists, aranidipine, efonidipine hydrochloride, nicardipine hydrochloride, barnidipine hydrochloride, benidipine hydrochloride, manidipine hydrochloride, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, amlodipine besilate, pranidipine, lercanidipine hydrochloride, isradipine, elgodipine, azelnidipine, lacidipine, vatanidipine hydrochloride, lemildipine, diltiazem hydrochloride, clentiazem maleate, verapamil hydrochloride, S-verapamil, fasudil hydrochloride, bepridil hydrochloride, gallopamil hydrochloride and the like are illustrated; as vasodilating antihypertensive agents, indapamide, todralazine hydrochloride, hydralazine hydrochloride, cadralazine, budralazine and the like are illustrated; as sympathetic blocking agents, amosulalol hydrochloride, terazosin hydrochloride, bunazosin hydrochloride, prazosin hydrochloride, doxazosin mesylate, propranolol hydrochloride, atenolol, metoprolol tartrate, carvedilol, nipradilol, celiprolol hydrochloride, nebivolol, betaxolol hydrochloride, pindolol, tertatolol hydrochloride, bevantolol hydrochloride, timolol maleate, carteolol hydrochloride, bisoprolol hemifumarate, bopindolol malonate, nipradilol, penbutolol sulfate, acebutolol hydrochloride, tilisolol hydrochloride, nadolol, urapidil, indoramin and the like are illustrated; as centrally acting antihypertensive agents, reserpine and the like are illustrated; and as $\alpha_2$-adrenoceptor agonists, clonidine hydrochloride, methyldopa, CHF-1035, guanabenz acetate, guanfacine hydrochloride, moxonidine, lofexidine, talipexole hydrochloride and the like are illustrated. These drugs are preferably used for hypertension.

[0073] As antiplatelets agents, ticlopidine hydrochloride, dipyridamole, cilostazol, ethyl icosapentate, sarpogrelate hydrochloride, dilazep dihydrochloride, trapidil, beraprost sodium, aspirin and the like are illustrated. Antiplatelets agents are preferably used for atherosclerosis or congestive heart failure.

[0074] As uric acid 'synthesis inhibitors, allopurinol, oxypurinol and the like are illustrated; as uricosuric agents, benzbromarone, probenecid and the like are illustrated; and as urinary alkalinizers, sodium hydrogen carbonate, potassium citrate, sodium citrate and the like are illustrated. These drugs are preferably used for hyperuricemia or gout.

[0075] In case of use in combination with drugs other than SGLT2 inhibitors, for example, in the use for diabetes , the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist and an appetite suppressant is preferable; the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue and an amylin agonist is more preferable; and the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer and an insulin preparation is most preferable. Similarly, in the use for diabetic complications , the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, hepatic gluconeogenesis inhibitor, D-chiroinsitol, glycogen synthase kinase-3 inhibitors, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a $\gamma$-aminobutyric acid antagonist, a sodium channel antagonist, a transcript factor NF-$\kappa$B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-$\alpha$-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, stilodexide, Y-128, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist and a diuretic agent is preferable; and the combination with at least one member of the group consisting of an aldose reductase inhibitor, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor and an angiotensin II receptor antagonist is more preferable. Furthermore, in the use for obesity, the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic glucone-

ogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, a $\beta_3$-adrenoceptor agonist and an appetite suppressant is preferable; and the combination with at least one member of the group consisting of a $\beta_3$-adrenoceptor agonist and an appetite suppressant is more preferable.

**[0076]** When the pharmaceutical compositions of the present invention are employed in the practical treatment, various dosage forms are used depending on their uses . As examples of the dosage forms, powders, granules, fine granules, dry syrups, tablets, capsules, injections, solutions, ointments, suppositories, poultices and the like are illustrated, which are orally or parenterally administered.

**[0077]** These pharmaceutical compositions can be prepared by admixing with or by diluting and dissolving an appropriate pharmaceutical additive such as excipients, disintegrators, binders, lubricants, diluents, buffers, isotonicities, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizing agents, dissolving aids and the like, and formulating the mixture in accordance with pharmaceutically conventional methods depending on their dosage forms. In case of the use of the compound of the present invention in combination with the drugs other than SGLT2 inhibitors, they can be prepared by formulating each active ingredient together or individually.

**[0078]** When the pharmaceutical compositions of the present invention are employed in the practical treatment, the dosage of a compound represented by the above general formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof as the active ingredient is appropriately decided depending on the age, sex, body weight and degree of symptoms and treatment of each patient, which is approximately within the range of from 0.1 to 1,000 mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 300 mg per day per adult human in the case of parenteral administration, and the daily dose can be divided into one to several doses per day and administered suitably. Also, in case of the use of the compound of the present invention in combination with the drugs other than SGLT2 inhibitors, the dosage of the compound of the present invention can be decreased depending on the dosage of the drugs other than SGLT2 inhibitors.

**[0079]** The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test Examples. However, the present invention is not limited thereto.

Reference Example 1

Methyl 4-(cyclopropylidenemethyl)benzoate

**[0080]** To a suspension of sodium hydride (60%, 0.27 g) in tetrahydrofuran (40 mL) was added cyclopropyltriphenylphosphonium bromide (2.6 6 g) , and the mixture was stirred at 70° C for 2 hours. To the reaction mixture was added methyl terephthalaldehydate (1.0 g), and the mixture was stirred at 70°C for 7 days. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/dichloromethane = 1/1) to give methyl 4-(cyclopropylidenemethyl)benzoate (0.80 g).

$^1$H-NMR ($CDCl_3$) δ ppm:
1.15-1.30 (2H, m), 1.40-1.50 (2H, m), 3.91 (3H, s), 6.75-6.85 (1H, m), 7.55-7.60 (2H, m), 7.95-8.05 (2H, m)

Reference Example 2

4 -(Cyclopropylidenemethyl)benzyl alcohol

**[0081]** To a suspension of lithium aluminum hydride (0.16 g) in tetrahydrofuran (30 mL) was added methyl 4-(cyclopropylidenemethyl)benzoate (0.80 g), and the mixture was stirred at room temperature for 5 hours. Water (0.4 mL) was added to the reaction mixture, and the mixture was stirred for 3 days. Insoluble materials were removed by filtration, and the solvent of the filtrate was removed under reduced pressure to give 4-(cyclopropylidenemethyl)benzyl alcohol (0.69 g).

$^1$H-NMR ($CDCl_3$) δ ppm:
1.15-1.25 (2H, m), 1.35-1.50 (2H, m), 1.61 (1H, t, J=6.0Hz), 4.68 (2H, d, J=6.0Hz), 6.70-6.80 (1H, m), 7.30-7.35 (2H, m), 7.50-7.55 (2H, m)

Example 1

5-Methyl-4-{[4-(cyclopropylidenemethyl)phenyl]methyl}-1,2-dihydro-3H-pyrazol-3-one

**[0082]** To a solution of 4-(cyclopropylidenemethyl)benzyl alcohol (0.21 g) and triethylamine (0.18 mL) in tetrahydro-

furan was added methanesulfonyl chloride (0.10 mL), and the mixture was stirred at room temperature for 30 minutes. Insoluble materials were removed by filtration. A solution of the obtained 4-(cyclopropylidenemethyl)benzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodiumhydride (60%, 0.052g) and methyl acetoacetate (0.14mL) in 1,2-dimethoxyethane, and the mixture was stirred at 70° C for 5 hours . To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. To a solution of the residue in toluene was added anhydrous hydrazine (0.12 mL), and the mixture was stirred at 95°C for 10 minutes. The solvent of the reaction mixture was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 5-methyl-4-{[4-(cyclopropylidenemethyl)phenyl]methyl}-1,2-dihydro-3H-pyrazol-3-one (0.032 g).

$^1$H-NMR (DMSO-$d_6$) δ ppm:

1.10-1.20 (2H, m), 1.30-1.45 (2H, m), 2.00 (3H, s). 3.52 (2H, s), 6.65-6.75 (1H, m), 7.05-7.15 (2H, m), 7.35-7.45 (2H, m)

Example 2

5-Methyl-4-{[4-(cyclopropylidenemethyl)phenyl]methyl}-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0083]** To a suspension of 5-methyl-4-{[4-(cyclopropylidene-methyl)phenyl]methyl}-1,2-dihydro-3*H*-pyrazol-3-one (0.026 g) and acetobromo-α-D-glucose (0.049 g) in tetrahydrofuran was added silver carbonate (0.036 g), and the mixture was stirred at 60° C overnight under light shielding. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran) and successively by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/3) to give 5-methyl-4-{[4-(cyclopropylidenemethyl)-phenyl]methyl}-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.010 g).

$^1$H-NMR ($CDCl_3$) δ ppm:

1.10-1.20 (2H, m), 1.30-1.45 (2H, m), 1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 3.50-3.70 (2H, m), 3.80-3.90 (1H, m), 4.13 ( 1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.1, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.65 (1H, m), 6.65-6.75 (1H, m), 7.05-7.15 (2H, m), 7.35-7.45 (2H, m)

Reference Example 3

4-Cyclopropylbenzaldehyde

**[0084]** To a solution of 4 -bromostylene (1.83g) in dichloromethane (5 mL) was added diethylzinc (1 mol/L, 30 mL) under an argon atmosphere at 0°C, and the-mixture was stirred at the same temperature for 10 minutes. Chloroiodomethane (4.3 mL) was added to the mixture, and the mixture was warmed to room temperature and stirred for 9 days. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give 4-cyclopropylbromobenzene. The obtained 4-cyclopropylbromobenzene was dissolved in tetrahydrofuran (25 mL) and cooled to -78°C. To the solution was added dropwise *tert*-butyl lithium (1.45 mol/L pentane solution, 9.4 mL) under an argon atmosphere, and the mixture was stirred at -78°C for 30 minutes. To the reaction mixture was added a solution of *N,N*-dimethylformamide (1.2 mL) in tetrahydrofuran (16 mL), and the mixture was warmed to 0°C and stirred for 1 hour. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 12/1) to give 4-cyclopropylbenzaldehyde (0.72 g).

$^1$H-NMR ($CDCl_3$) δ ppm:

0.60-0.75 (2H, m), 1.05-1.15 (2H, m), 1.80-1.95 (1H, m), 7.15-7.25 (2H, m), 7.7'0-7.80 (2H, m), 9.94 (1H, s)

Reference Example 4

4-Cyclopropylbenzyl alcohol

**[0085]** To a solution of 4-cyclopropylbenzaldehyde (0.71 g) in methanol (10 mL) was added lithium borohydride (2 mol/L tetrahydrofuran solution, 3.7 mL), and the mixture was warmed to room temperature and stirred for 30 minutes. To the reaction mixture was added water, and the mixture was extracted with diethyl ether. The organic layer was washed with 1 mol/L hydrochloric acid solution and brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/

ethyl acetate = = 5/1) to give 4-cyclopropylbenzyl alcohol (0.69 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
0.60-0.75 (2H, m), 0.90-1.00 (2H, m), 1.80-1.95 (1H, m), 4.62 (2H, s), 7.00-7.10 (2H, m), 7.20-7.30 (2H, m)

Example 3

5-Methyl-4-[(4-cyclopropylphenyl)methyl]-1,2-dihydro-3*H*-pyrazol-3-one

**[0086]** To a solution of 4-cyclopropylbenzyl alcohol (1.1 g) in tetrahydrofuran (23 mL) were added triethylamine (1.2 mL) and methanesulfonyl chloride (0.66 mL), and the mixture was stirred at room temperature for 2 hours. Insoluble materials were removed by filtration. A solution of the obtained 4-cyclopropylbenzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride ( 60% , 0.34 g) and methyl acetoacetate (0.91 mL) in 1,2-dimethoxyethane (26 mL), and the mixture was stirred at 80°C for 13 hours. Into the reaction mixture was poured a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in toluene (23mL), to the solution was added hydrazine monohydrate (1.1 mL), and the mixture was stirred at 100° C for 10 hours. After cooling to room temperature, resulting insoluble materials was collected by filtration, washed with water and then hexane and dried under reduced pressure to give 5-methyl-4-[(4-cyclopropylphenyl)methyl]-1,2-dihydro-3*H*-pyrazol-3-one (1.22 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
0.50-0.65 (2H, m), 0.80-0.95 (2H, m), 1.75-1.90 (1H, m), 2.01 (3H, s), 3.58 (2H, s), 6.85-7.10 (4H, m)

Example 4

5-Methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0087]** To a suspension of 5-methyl-4-[(4-cyclopropylphenyl)-methyl]-1,2-dhydro-3*H*-pyrazol-3-one (0.23 g) and acetobromo-α-D-glucose (0.45 g) in tetrahydrofuran (5 mL) was added silver carbonate (0.33 g), and the mixture was stirred at 40° C for 36 hours under light shielding. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran) and successively by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/2) to give 5-methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.30 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
0.55-0.70 (2H, m) , 0.85-1.00 (2H, m) , 1.75-1.90 (1H, m) , 1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.54 (1H, d, J=15.8Hz), 3.61 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.12 (1H, dd, J=2.3, 12.4Hz) , 4.30 (1H, dd, J=4.1, 12.4Hz) , 5.15-5.35 (3H, m), 5.50-5.65 (1H, m), 6.85-7.05 (4H, m)

Reference Example 5

Methyl (*E*)-4-(but-1-en-1-yl)benzoate

**[0088]** To a suspension of sodium hydride (60%, 0.97 g) in tetrahydrofuran (80 mL) was added methyl 4-(diethylphosphorylmethyl)benzoate (5.8 g) at 0°C, and the mixture was stirred for 30 minutes. To the reaction mixture was added a solution of propionaldehyde (1.6 mL) in tetrahydrofuran (10 mL), and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/1) to give methyl (*E*)-4-(but-1-en-1-yl)benzoate (2.5 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
1.11 (3H, t, J=7.5Hz), 2.20-2.35 (2H, m) , 3.90 (3H, s), 6.35-6.45 (2H, m), 7.35-7.45 (2H, m), 7.90-8.00 (2H, m)

Reference Example 6

(*E*)-4-(But-1-en-1-yl)benzyl alcohol

**[0089]** To a suspension of lithium aluminum hydride (1.2 g) in diethyl ether (100 mL) was added a solution of methyl 4-(but-1-en-1-yl)benzoate (2.5 g) in diethyl ether (20 mL) at 0°C, and the mixture was heated under reflux for 30 mixture. After the reaction mixture was cooled to 0°C, to the mixture were added water (1.2 mL), an aqueous sodium hydroxide

solution (15%, 1.2 mL) and water (3.6 mL), and the mixture was stirred at room temperature for 5 minutes. Insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 2/1) to give (E)-4-(but-1-en-1-yl)benzyl alcohol (1.9 g).

$^1$H-NMR ($CDCl_3$) δ ppm:
1.09 (3H, t, J=7.5Hz), 1.60 (1H, t, J=6.0Hz), 2.15-2.30 (2H, m), 4.66 (2H, d, J=6.0Hz), 6.27 (1H, dt, J=15.9, 6.3Hz), 6.37 (1H, d, J=15.9Hz), 7.25-7.40 (4H, m)

Example 5

(*E*)-4-{[4-(But-1-en-1-yl)phenyl]methyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3*H*-one

**[0090]** The title compound was prepared in a similar manner to that described in Example 3 using 4-(but-1-en-1-yl) benzyl alcohol instead of 4-cyclopropylbenzyl alcohol.

$^1$H-NMR (DMSO-$d_6$) δ ppm:
1.03 (3H, t, J=7.5Hz), 1.99 (3H, s), 2.10-2.25 (2H, m), 3.51 (2H, s), 6.23 (1H, dt, J=16.0, 6.2Hz), 6.32 (1H, d, J=16.0Hz), 7.05-7.10 (2H, m), 7.20-7.30 (2H, m)

Example 6

(*E*)-4-{[4-(But-1-en-1-yl)phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0091]** The title compound was prepared in a similar manner to that described in Example 4 using (E)-4-{[4-(but-1-en-1-yl)phenyl]methyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-1,2-dihydro-3H-pyrazol-3-one.

$^1$H-NMR ($CDCl_3$) δ ppm:
1.07 (3H, t, J=7.3Hz), 1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.10-2.25 (2H, m), 3.57 (1H, d, J=15.6Hz), 3.63 (1H, d, J=15.6Hz), 3.80-3.90 (1H, m), 4.05-4.20 (1H, m), 4.31 (1H, dd, J=4.0, 12.3Hz), 5.15-5.35 (3H, m), 5.50-5.65 (1H, m), 6.10-6.25 (1H, m), 6.25-6.35 (1H, m), 6.95-7.10 (2H, m), 7.15-7.25 (2H, m)

Reference Example 7

1-Bromo-4-[(methoxymethyloxy)methyl]benzene

**[0092]** To a solution of 4-bromobenzyl alcohol (2.8 g) and diisopropylethylamine (2.5 g) in dichloromethane (30 mL) was added chloromethyl methyl ether (1.3 g) at 0°C, and the mixture was stirred at room temperature for 14 hours. To the reaction mixture was water, and the mixture was extracted diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/1) to give 1-bromo-4-[(methoxymethyloxy)methyl]benzene (3.0 g).

$^1$H-NMR ($CDCl_3$) δ ppm:
3.40 (3H, s), 4.54 (2H, s), 4.70 (2H, s), 7.20-7.30 (2H, m), 7.45-7.55 (2H, m)

Reference Example 8

4-(Thiazol-2-yl)benzyl alcohol

**[0093]** To a solution of 1-bromo-4-[(methoxymethyloxy)-methyl] benzene (3.0 g) in tetrahydrofuran (52 mL) was added n-butyllithium (1.6 mol/L hexane solution, 9.3 mL) at -78°C, and the mixture was stirred for 30 minutes. To the reaction mixture was added /triisopropyl borate (2.6 g), and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 1 mol/L hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 4-[(methoxymethyloxy)methyl]phenylboric acid (2.5 g). A mixture of the obtained 4-[(methoxymethyloxy)methyl]-phenylboric acid (2.5 g), 2-bromothiazole (1.2 g), cesium fluoride (2.2 g) and tetrakis (triphenylphosphine) palladium (0) (0.16 g) in 1,2-dimethoxyethane (40 mL), ethanol (10 mL) and water (10 mL) was stirred at 85°C for 24 hours. The reaction mixture was concentrated under reduced pressure, and to the residue was added water, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified

by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/1) to give 2-{4-[(methoxymethyloxy)methyl] phenyl}thiazole (0.80 g). To a solution of 2-{4-[(methoxymethyloxy)-methyl]phenyl}thiazole (0.80 g) in ethanol (10 mL) was added 2 mol/L hydrochloric acid solution (5 mL), and the mixture was stirred at 50°C for 5 hours. Concentrated hydrochloric acid (0.10 mL) was added to the mixture, and the mixture was stirred for 1 hour. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate=2/1-1/1) to give 4-(thiazol-2-yl)benzyl alcohol (0.33 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
4.76 (2H, d, J=4.6Hz), 7.33 (1H, d, J=3.7Hz), 7.40-7.50 (2H, m), 7.87 (1H, d, J=3.7Hz), 7.90-8.05 (2H, m)

Example 7

5-Methyl-4-([4-(thiazol-2-yl)phenyl]methyl}-1,2-dihdro-3*H*-pyrazol-3-one

**[0094]** The title compound was prepared in a similar manner to that described in Example 3 using 4- (thiazol-2-yl) benzyl alcohol instead of 4-cyclopropylbenzyl alcohol.
$^1$H-NMR (DMSO-$d_6$) δ ppm:
2.03 (3H, s) 3.60 (2H, s) , 7.25-7.30 (2H, m) , 7.74 (1H, d, J=3.1Hz) 7.80-7.85 (2H, m), 7.88 (1H, d, J=3.1Hz)

Example 8

5-Methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-4-{[4-(thiazol-2-yl)phenyl]methyl}-1*H*-pyrazole

**[0095]** The title compound was prepared in a similar manner to that described in Example 4 using 5-methyl-4-([4-(thiazol-2-yl)phenyl]methyl}-1,2-dihydro-3*H*-pyrazol-3-one instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-1,2-dihydro-3*H*-pyrazol-3-one.
$^1$H-NMR ($CDCl_3$) δ ppm:
1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.13 (3H, s), 3.64 (1H, d, 3=16.0Hz), 3.71 (1H, d, 3=16.0Hz), 3.80-3.90 (1H, m) , 4.14 (1H, dd, J=2.7, 12.2Hz) , 4.32 (1H, dd, J=3.8, 12.2Hz) , 5.15-5.35 (3H, m) , 5.55-5.65 (1H, m), 7.15-7.25 (2H, m), 7.29 (1H. d, J=3.2Hz), 7.80-7.90 (3H, m)

Reference Examples 9

4-[3-(Benzyloxy)propyl]benzyl alcohol

**[0096]** To a solution of ethyl diethylphosphonoacetate (4.4 mL) in tetrahydrofuran (40 mL) was added sodium hydride (60%, 0.88 g) at 0°C, and the mixture was stirred for 10 minutes. To the reaction mixture was added a solution of terephthalaldehyde *mono*-(diethyl acetal) (4.2 g) in tetrahydrofuran (10 mL), and the mixture was stirred at room temperature for 1.5 hours. To the reaction mixture were added a saturated aqueous ammonium chloride solution and water, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1) to give ethyl 4-(diethoxymethyl)cinnamate (5.8 g). To a solution of the obtained ethyl 4-(diethoxymethyl)cinnamate (5.8 g) in tetrahydrofuran (50 mL) was added 5% platinum on carbon powder (0.58 g), and the mixture was stirred at room temperature under a hydrogen atmosphere for 10 hours. Insoluble materials was removed by filtration, and the filtrate was concentrated under reduced pressure. A solution of the residue in tetrahydrofuran (20 mL) was added to a suspension of lithium aluminum hydride (1.1 g) in tetrahydrofuran (100 mL) at 0°C. The reaction mixture was heated at 70°C and stirred for 40 minutes . After the reaction mixture was cooled to 0°C, water (1.1 mL), 15% aqueous sodium hydroxide solution (1.1 mL) and water (3.3 mL)were added, and the mixture was stirred at room temperature for 10 minutes. Insoluble materials were removed by filtration, and the solvent of the filtrate was removed under reduced pressure to give 4- (3-hydroxypropyl)benzaldehyde diethyl acetal (4.7g). To a solution of the obtained 4-(3-hydroxypropyl)benzaldehyde diethyl acetal (4.7 g) in dimethylformamide (100 mL) was added sodium hydride (60%, 1.2 g) at 0°C, and the mixture was stirred for 5 minutes. To the reaction mixture was added benzyl bromide (2.5 mL), and the mixture was stirred at room temperature for 72 hours. Water was added to the reaction mixture, and the mixture was extracted with hexane. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 4-[3-(benzyloxy)propyl]benzaldehyde diethyl acetal (6.4 g). To a solution of the obtained 4-[3-(benzyloxy)propyl]-benzaldehyde diethyl acetal (6.4 g) in tetrahydrofuran (60 mL) was added 2 mol/L hydrochloric acid solution (10 mL) at 0°C, and the mixture was stirred for 1 hour. To the reaction mixture was added water, and the mixture was extracted with diethyl

ether. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in ethanol (50 mL), and to the solution was added sodium borohydride (1.1 g) at 0°C. The mixture was stirred for 14 hours while gradually returning to room temperature. To the reaction mixture was added methanol, and the mixture was concentrated under reduced pressure. To the residue was added ethyl acetate, and the mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1 - 2/1) to give 4-[3-(benzyloxy) propyl]benzyl alcohol (3.7 g).

$^1$H-NMR ($CDCl_3$) δ ppm:

1.85-2.00 (2H, m);, 2.65-2.80 (2H, m), 3.49 (2H, t, J=6.4Hz), 4.51 (2H, s), 4.66 (2H, d, J=5.7Hz), 7.15-7.40 (9H, m)

Example 9

4-({4-[3-(Benzyloxy)propyl]phenyl}methyl)-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one

**[0097]** To a solution of 4-[3-(benzyloxy)propyl]benzyl alcohol (2.0g) in tetrahydrofuran (26 mL) were added triethylamine (1.1 mL) and methanesulfonyl chloride (0.60mL) at 0°C, and the mixture was stirred at room temperature for 2 hours. Insolublematerials was removed by filtration. A solution of the obtained 4-[3-(benzyloxy)propyl]benzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride (60%, 0.31 g) and ethyl 4,4,4-trifluoroacetoacetate (1.1 mL) in 1, 2-dimethoxyethane (26 mL), and the mixture was stirred at 80°C for 16 hours. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with diethyl ether. The extract was washed with water and dried over anhydrous magnesium sulfate . The solvent was removed under reduced pressure, and the residue was dissolved in toluene (20 mL). To the solution was added anhydrous hydrazine (0.74 mL), and the mixture was stirred at 80°C for 18 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) and successively by column chromatography on silica gel (eluent: dichloromethane/methanol = 20/1) to give 4-({4-[3-(benzyloxy)propyl]phenyl}methyl)-5-trifluoromethyl-1,2-dihydro-3H-pyrazol-3-one (0.84 g).

$^1$H-NMR ($CDCl_3$) δ ppm:

1.85-1.95 (2H, m);, 2.60-2.70 (2H, m), 3.48 (2H, t, J=6.5Hz), 3.79 (2H, s), 4.49 (2H, s), 7.05-7.20 (4H, m), 7.25-7.40 (5H, m)

Example 10

4-({4-[3-(Benzyloxy)propyl]phenyl}methyl)-5-trifluoromethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0098]** To a solution of 4-({4-[3-(benzyloxy)propyl]phenyl}methyl)-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one (0.83g) and acetobromo-α-D-glucose (1.5 g) in acetonitrile (12 mL) was added potassium carbonate (0.55 g), and the mixture was stirred at 60°C for 20 hours. Insoluble materials were removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/1-1/2) to give 4-({4-[3-(benzyloxy)propyl]phenyl}methyl)-5-trifluoromethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.64 g).

$^1$H-NMR ($CDCl_3$) δ ppm:

1.80-1.95 (5H, m), 2.02 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.60-2.70 (2H, m), 3.47 (2H, t, J=6.2Hz), 3.74 (2H, s), 3.75-3.85 (1H, m), 4.18 (1H, dd, 2.2, 12.7Hz), 4.26 (1H, dd, 4.5, 12.7Hz), 4.50 (2H, s), 5.15-5.35 (3H, m), 5.35-5.45 (1H, m), 7.00-7.15 (4H, m), 7.20-7.40 (5H, m)

Example 11

4-{[4-(3-Hydroxypropyl)phenyl]methyl}-5-trifluoromethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0099]** To a solution of 4-{[4-(3-benzyloxy)propyl]phenyl}methyl)-5-trifluoromethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.64 g) in methanol (10mL) was added 10% palladium-carbon powder (0.13 g), and the mixture was stirred at room temperature under a hydrogen atmosphere for 11 hours. Insoluble materials were removed by filtration, the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/2) to give 4-{[4-(3-hydroxypropyl)phenyl]methyl)-5-trifluoromethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.45 g).

$^1$H-NMR ($CDCl_3$) δ ppm:
1.80-1.90 (2H, m), 1.92 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 2.60-2.70 (2H, m), 3.65 (2H, t, J=6.3Hz), 3.75 (2H, s), 3.75-3.85 (1H, m), 4.15-4.30 (2H, m), 5.10-5.40 (4H, m), 7.05-7.15 (4H, m)

Reference Example 10

4-(2-Methylprop-1-en-1-yl)benzyl alcohol

**[0100]** To a suspension of isopropyltriphenylphosphonium iodide (9.5 g) in tetrahydrofuran (90 mL) was added *n*-butyllithium (1.5 mol/L hexane solution, 15 mL) at 0°C , and the mixture was stirred for 15 minutes. To the reaction mixture was added a solution of methyl terephthalaldehydate (3.3 g) in tetrahydrofuran (10 mL), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into a saturated aqueous ammonium chloride solution, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on aminopropyl silica gel (eluent: hexane/ethyl acetate = 3/1) and then by column chromatography on silica gel (eluent: dichloromethane/ethyl acetate = 10/1) to give methyl 4-(2-methylprop-1-en-1-yl)-benzoate (3.4 g) . To a suspension of lithium aluminum hydride (0.68 g) in diethyl ether (120 mL) was added a solution of methyl 4-(2-methylprop-1-en-1-yl) benzoate (3.4g) indiethyl ether (30 mL ) at 0°C, and the mixture was heated under reflux for 50 minutes. After the reaction mixture was cooled to 0°C, water (0.69 mL), 15% aqueous sodium hydroxide solution (0.69 mL) and water (2 mL) were added, and the mixture was stirred at room temperature for 30 minutes. Insoluble materials were removed by filtrate, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = = 4/1 - 2/1) to give 4-(2-methylprop-1-en-1-yl)benzyl alcohol. (2.8 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
1.60 (1H, t, J=5.6Hz), 1.86 (3H, s). 1.90 (3H, s), 4.67 (2H, d, J=5.6Hz), 6.26 (1H, s), 7.15-7.25 (2H, m), 7.25-7.35 (2H, m)

Example 12

5-Methyl-4-{[4-(2-methylprop-1-en-1-yl)phenyl]methyl}-1,2-dihydro-3*H*-pyrazol-3-one

**[0101]** To a solution of 4-(2-methylprop-1-en-1-yl)benzyl alcohol (0.60 g) and carbon tetrabromide (1.2 g) in dichloromethane (12 mL) was added triphenylphosphine (0.97 g) at 0°C, and the mixture was stirred at room temperature for 3.5 hours. To the reaction mixture was added water, and the mixture was extracted with hexane. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane) to give 4-(2-methylprop-1-en-1-yl)benzyl bromide. To a solution of methyl acetoacetate (0.44 mL) in tetrahydrofuran (17 mL) was added sodium hydride (60%, 0.18 g) at 0°C, and the mixture was stirred for 10 minutes. To the reaction mixture was added a solution of 4-(2-methylprop-1-en-1-yl)benzyl bromide in tetrahydrofuran (3 mL), and the mixture was heated under reflux for 3.5 hours. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (8 mL). To the solution was added hydrazine monohydrate (0.54 mL), and the mixture was stirred at 80°C for 30 minutes. The reaction mixture was cooled to 0°C, and the resulting precipitates were collected by filtration, washed with water and hexane, and dried under reduced pressure to give 5-methyl-4-{[4-(2-methylprop-1-en-1-yl)phenyl]methyl}-1,2-dihydro-3H-pyrazol-3-one (0.31 g).
$^1$H-NMR (DMSO-$d_6$) δ ppm:
1.79 (3H, d, J=0.8Hz), 1.85 (3H, d, J=1.3Hz), 2.01 (3H, s), 3.52 (2H, s), 6.15-6.25 (1H, m), 7.05-7.15 (4H, m)

Example 13

5-Methyl-4-{[4-(2-methylprop-1-en-1-yl)phenyl]methyl}-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0102]** The title compound was prepared in a similar manner to that described in Example 4 using 5-methyl-4-{[4-(2-methyl-prop-1-en-1-yl)phenyl]methyl}-1,2-dihydro-3*H*-pyrazol-3-one instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-1,2-dihydro-3H-pyrazol-3-one.
$^1$H-NMR ($CDCl_3$) 6 ppm:
1.83 (3H, s), 1.86 (3H, s), 1.87 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.12 (3H, s), 3.57 (1H, d, J=15.6Hz),

3.65 (1H, d, J=15.6Hz), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.1, 12.6Hz), 4.31 (1H, dd, J=3.9, 12.6Hz), 5.15-5.35 (3H, m), 5.50-5.65 (1H, m), 6.15-6.25 (1H, m), 7.00-7.15 (4H, m)

Reference Example 11

4-[(4-Bromophenyl)methyl]-5-methyl-1,2-dihdro-3*H*-pyrazol-3-one

**[0103]** To a solution of methyl acetoacetate (3.2 mL) in tetrahydrofuran (100 mL) was added sodium hydride (60%, 1.3 g) at 0°C, and the mixture was stirred for 5 minutes. To the reaction mixture was added 4-bromobenzyl bromide (7.5 g), and the mixture was heated under reflux for 3 hours. To the reaction mixture was added water, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (50 mL). To the solution was added hydrazine monohydrate (4.4 mL), and the mixture was stirred at 80°C for 30 minutes. The reaction mixture was cooled to room temperature, and the resulting precipitates were collected by filtration, washed with water and hexane, and dried under reduced pressure to give 4-[(4-bromophenyl)methyl]-5-methyl-1,2-dihdro-3H-pyrazol-3-one (4.0 g).
$^1$H-NMR (DMSO-$d_6$) δ ppm:
2.00 (3H, s), 3.52 (2H/ s), 7.05-7.15 (2H, m), 7.35-7.45 (2H, m)

Reference Example 12

4-[(4-Bromophenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0104]** The title compound was prepared in a similar manner to that described in Example 4 using 4-[(4-bromophenyl)-methyl]-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-1,2-dihydro-3*H*-pyrazol-3-one.
$^1$H-NMR ($CDCl_3$) δ ppm:
1.89 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.12 (3H, s), 3.54 (1H, d, J=16.0Hz), 3.60 (1H, d, J=16.0Hz), 3.80-3.90 (1H, m), 4.05-4.20 (1H, m), 4.31 (1H, dd, J=3.3, 12.3Hz), 5.10-5.35 (3H, m), 5.55-5.65 (1H, m), 6.95-7.10 (2H, m), 7.30-7.40 (2H, m)

Example 14

4-([4-(4-Fluorophenyl)phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0105]** A mixture of 4-[(4-bromophenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.099 g), 4-fluorophenylboronicacid (0.046 g), cesiumfluoride (0.050 g) and tetrakis(triphenylphosphine)palladium (0) (0.0038 g) in 1,2-dimethoxyethane (1.3 mL), ethanol (0.3 mL) and water (0.3 mL) was stirred at 85°C for 18 hours. The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 1/1-1/2-1/5) to give 4-([4-(4-fluoro-phenyl)phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.061 g).
$^1$H-NMR ($CDCl_3$) 6 ppm:
1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.16 (3H, s) , 3.64 (1H, d, J=15.9Hz) , 3.70 (1H, d, 3=15.9Hz), 3.80-3.90 (1H,m), 4.14 (1H, dd, 3=2.0,12.5Hz), 4.31 (1H, dd, 3=4.1,12.5Hz), 5.15-5.30 (3H, m), 5.55-5.65 (1H, m), 7.05-7.15 (2H, m), 7.15-7.25 (2H, m), 7.35-7.55 (4H, m)

Reference Example 13

4-Cyclobutyloxybenzyl alcohol

**[0106]** To a suspension of 4-hydroxybenzaldehyde (0.12 g) and cesium carbonate (0.49 g) in *N,N*-dimethylformamide (2 mL) was added cyclobutyl bromide (0.15 g), and the mixture was stirred at 65°C overnight. To the reaction mixture was added 1 mol/L aqueous sodium hydroxide solution, and the mixture was extracted with diethyl ether. The organic layer was washed with 0.5 mol/L aqueous sodium hydroxide solution, water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 4-cyclobutyloxybenzaldehyde (0.13 g). To a solution of the obtained 4-cyclobutyloxybenzaldehyde (0.13 g) in methanol (10 mL) was added sodium borohydride (0.056 g), and the mixture was stirred at room temperature overnight. To the reaction mixture was added 1 mol/L hydrochloric acid solution, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous

magnesium sulfate, and the solvent was removed under reduced pressure to give 4-cyclobutyloxybenzyl alcohol (0.12 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
1.50 (1H, t, J=5.8Hz), 1.60-1.75 (1H, m), 1.80-1.95 (1H, m), 2.10-2.25 (2H, m), 2.40-2.50 (2H, m), 4.61 (2H, d, J=5.8Hz), 4.60-4.70 (1H, m), 6.75-6.85 (2H, m), 7.20-7.30 (2H, m)

Example 15

4-{[4-(Cyclobutyloxy)phenyl]methyl}-5-methyl-1,2-dihdro-3*H*-pyrazol-3-one

**[0107]** The title compound was prepared in a similar manner to that described in Example 3 using 4-cyclobutyloxybenzyl alcohol instead of 4-cyclopropylbenzyl alcohol.
$^1$H-NMR (DMSO-$d_6$) δ ppm:
1.55-1.70 (1H, m), 1.70-1.85 (1H, m), 1.90-2.05 (5H, m), 2.30-2.45 (2H, m), 3.50 (2H, s), 4.55-4.65 (1H, m), 6.65-6.75 (2H, m), 6.95-7.10 (2H, m)

Example 16

4-{[4-(Cyclobutyloxy)phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0108]** The title compound was prepared in a similar manner to that described in Example 4 using 4-{[4-(cyclobutyloxy)phenyl]methyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-1,2-dihydro-3*H*-pyrazol-3-one.
$^1$H-NMR ($CDCl_3$) δ ppm:
1.55-1.95 (2H, m), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.00-2.25 (2H, m), 2.35-2.50 (2H, m), 3.52 (1H, d, J=15.6Hz), 3.58 (1H, d, J=15.6Hz), 3.80-3.90 (1H, m) , 4.12 (1H, dd, 3=2.4, 12.3Hz), 4.30 (1H, dd, 3=3.7, 12.3Hz), 4.50-4.65 (1H,m),5.15-5.35 (3H,m), 5.50-5.60(1H,m), 6.65-6.75 (2H, m), 6.95-7.05 (2H, m)

Reference Example 14

4-({4-[4-(Benzyloxy)phenyl]phenyl}methyl)-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0109]** The title compound was prepared in a similar manner to that described in Example 14 using 4-(benzyloxy) phenylboronic acid instead of 4-fluorophenylboronic acid.
$^1$H-NMR ($CDCl_3$) δ ppm:
1.85 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.15 (3H, s), 3.62(1H, d, J=16.0Hz), 3.69(1H, d, J=16.0Hz), 3.80-3.90 (1H, m), 4.10-4.20 (1H, m), 4.25-4.40 (1H, m), 5.10 (2H, s), 5.15-5.35 (3H, m), 5.55-5.65 (1H, m), 6.95-7.55 (13H, m)

Example 17

4-{[4-(4-Hydroxyphenyl)phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0110]** To a solution of 4-({4-[4-(benzyloxy)phenyl]phenyl}methyl)-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.14 g) in methanol (3 mL) was added 10% palladium-carbon powder (0.030 g), and the mixture was stirred at room temperature under a hydrogen atmosphere for 11 hours. Insoluble materials were removed by filtration, and the solvent of the filtrate was removed under reduced pressure . The residue was purified by column chromatography on aminopropyl silica gel (eluent: hexane/ethyl acetate = = 1/1 - 1/5 - dichloromethane/methanol = 10/1) to give 4-{[4-(4-hydroxyphenyl)phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.071 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
1.85 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.15 (3H, s), 3.62 (1H, d, J=15.7Hz), 3.69 (1H, d, J=15.7Hz), 3.80-3.90 (1H, m), 4.10-4.20 (1H, m) , 4.31 (1H, dd, J=3.9, 12.6Hz), 5.12 (1H, brs), 5.15-5.35 (3H, m), 5.55-5.65 (1H, m), 6.80-6.90 (2H, m), 7.10-7.25 (2H, m), 7.35-7.50 (4H, m)

Example 18

4-{[4-(3-Fluorophenyl)phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0111]** The title compound was prepared in a similar manner to that described in Example 14 using 3-fluorophenylboronic acid instead of 4-fluorophenylboronic acid.
$^1$H-NMR ($CDCl_3$) δ ppm:
1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.16 (3H, s) , 3.63 (1H, d, J=16.1Hz) , 3.71(1H,d, J=16.1Hz) , 3.80-3.90 (1H, m), 4.05-4.20 (1H, m), 4.32 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.55-5.65 (1H, m), 6.95-7.05 (1H, m), 7.15-7.50 (7H, m)

Reference Example 15

4-(Pyridin-2-yl)benzyl chloride

**[0112]** To a solution of 2-(*p*-tolyl)pyridine (1.7 g) and N-chlorosuccinimide (1.5 g) in carbon tetrachloride ( 30 mL ) was added α,α-azobisisobutyronitrile (0.033 g), and the mixture was heated under reflux for 5 hours. Insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/1 - 3/1) to give 4-(pyridin-2-yl)benzyl chloride (1.1 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
4.65 (2H, s), 7.20-7.30 (1H, m), 7.45-7.55 (2H, m), 7.65-7.80 (2H, m), 7.95-8.05 (2H, m), 8.65-8.75 (1H, m)

Example 19

5-Methyl-4-{[4-(pyridin-2-yl)phenyl]methyl}-1,2-dihydro-3*H*-pyrazol-3-one

**[0113]** The title compound was prepared in a similar manner to that described in Reference Example 11 using 4-(pyridin-2-yl)benzyl chloride instead of 4-bromobenzyl bromide.
$^1$H-NMR (DMSO-$d_6$) δ ppm:
2.03 (3H, s), 3.60 (2H, s), 7.20-7.30 (2H, m), 7.31 (1H, ddd, J=1.2, 4.7, 7.3Hz), 7.80-8.00 (4H, m), 8.63 (1H, ddd, J=0.9, 1.6, 4.7Hz)

Example 20

3-(β-D-Glucopyranosyloxy)-5-methyl-4-{[4-(cyclopropylidene-methyl)phenyl]methyl}-1*H*-pyrazole

**[0114]** A solution of 5-methyl-4-{[4-(cyclopropylidene-methyl)phenyl]methyl}-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0 .010 g) in methanol ( 2 mL) was added sodium methoxide (28% methanol solution, 0.0020 mL), and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol) to give 3-(β-D-glucopyranosyloxy)-5-methyl-4-{[4-(cyclopropylidene-methyl)phenyl]methyl)-1*H*-pyrazole (0.0070 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.05-1.20 (2H, m), 1.30-1.45 (2H, m), 2.06 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10 (1H, m), 6.60-6.70 (1H, m), 7.00-7.20 (2H, m), 7.30-7.45 (2H, m)

Example 21

3-(β-D-Glucopyranosyloxy)-5-methyl-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole

**[0115]** To a solution of 5-methyl-4-[(4-cyclopropylphenyl)-methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.14 g) in ethanol (8.4 mL) was added 2 mol/L aqueous sodium hydroxide solution (0.63 mL), and the mixture was stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 6/1) to give 3-(β-D-glucopyranosyloxy)-5-methyl-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole (0.087 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
0.55-0.70 (2H, m), 0.85-0.95 (2H, m), 1.75-1.90 (1H, m), 2.04 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10

(1H, m), 6.85-7.15 (4H, m)

Example 22

(E)-4-{[4-(But-1-en-1-yl)phenyl]methyl}-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

**[0116]** The title compound was prepared in a similar manner to that described in Example 21 using (*E*)-4-([4-(but-1-en-1-yl)-phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
$^1$H-NMR ($CD_3OD$) δ ppm:
1.07 (3H, t, J=7.4Hz), 2.05 (3H, s), 2.15-2.25 (2H,m), 3.30-3.45 (4H, m), 3.60-3.80 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 6.22 (1H, dt, J=16.0. 6.5Hz), 6.33 (1H, d, J=16.0Hz), 7.05-7.15 (2H, m), 7.20-7.25 (2H, m)

Example 23

3-(β-D-Glucopyranosyloxy)-5-methyl-4-([4-(thiazol-2-yl)-phenyl]methyl}-1*H*-pyrazole

**[0117]** The title compound was prepared in a similar manner to that described in Example 21 using 5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-4-{[4-(thiazol-2-yl)-phenyl]methyl)-1*H*-pyrazole instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
$^1$H-NMR ($CD_3OD$) 6 ppm:
2.10 (3H, s), 3.25-3.50 (4H, m), 3.60-3.90 (4H, m), 5.05-5.15 (1H, m), 7.30-7.40 (2H, m), 7.55 (1H, d, J=3.1Hz), 7.80-7.90 (3H, m)

Example 24

3-(β-D-Glucopyranosyloxy)-4-{[4-(3-hydroxypropyl)phenyl]-methyl} -5-trifluoromethyl-1*H*-pyrazole

**[0118]** To a solution of 4-([4-(3-hydroxypropyl)phenyl]methyl}-5-trifluoromethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.45 g) in methanol (7 mL) was added sodium methoxide (28% methanol solution, 0.068 mL), and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 6/1) to give 3-(β-D-glucopyranosyloxy)-4-{[4-(3-hydroxypropyl)phenyl]methyl)-5-trifluoromethyl-1*H*-pyrazole (0.17 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.75-1.85 (2H, m), 2.62 (2H, t, J=7.6Hz), 3.30-3.45 (4H, m), 3.54 (2H, t, J=6.2Hz), 3.68 (1H, dd, J=5.2, 12.2Hz), 3,75-3.95 (3H, m), 4.95-5.05 (1H, m), 7.05-7.15 (4H, m)

Example 25

3-(β-D-Glucopyranosyloxy)-5-methyl-4-([4-(2-methylprop-1-en-1-yl )phenyl]methyl}-1*H*-pyrazole

**[0119]** The title compound was prepared in a similar manner to that described in Example 21 using 5-methyl-4-{[4-(2-methylprop-1-en-1-yl)phenyl]methyl}-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
$^1$H-NMR ($CDCl_3$) δ ppm:
1.81 (3H, d, J=1.0Hz), 1.86 (3H, s), 2.06 (3H, s), 3.25-3.45 (4H, m), 3.60-3.80 (3H, m), 3.80-3.90 (1H, m); 5.00-5.10 (1H, m), 6.15-6.25 (1H, m), 7.00-7.20 (4H, m)

Example 26

4-{[4-(4-Fluorophenyl)phenyl]methyl}-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

**[0120]** The title compound was prepared in a similar manner to that described in Example 21 using 4-{[4-(4-fluorophenyl)-phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-B-D-glucopyranosyloxy)-1*H*-pyrazole.
$^1$H-NMR ($CD_3OD$) δ ppm:
2.10 (3H, s), 3.30-3.45 (4H, m), 3.60-3.90 (4H, m), 5.05-5.15 (1H, m), 7.05-7.20 (2H, m), 7.25-7.35 (2H, m), 7.40-7.50

(2H, m), 7.50-7.65 (2H, m)

Example 27

4-{[4-(Cyclobutyloxy)phenyl]methyl}-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

**[0121]** The title compound was prepared in a similar manner to that described in Example 21 using 4-{[4-(cyclobutyloxy)-phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
$^1$H-NMR ($CD_3OD$) δ ppm:
1.60-1.90 (2H, m), 2.00-2.15 (5H, m), 2.35-2.50 (2H, m), 3.30-3.45 (4H, m), 3.60-3.75 (3H, m), 3.75-3.90 (1H, m), 4.50-4.70 (1H, m), 5.00-5.10 (1H, m), 6.65-6.75 (2H, m), 7.00-7.15 (2H, m)

Example 28

3-(β-D-Glucopyranosyloxy)-5-methyl-1-isopropyl-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole

**[0122]** To a suspension of 3-(β-D-glucopyranosyloxy)-5-methyl -4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole (56 mg) and cesium carbonate (23 mg) in *N,N*-dimethylformamide (1.5 mL) was added 2-iodopropane (0.043 mL) at 80°C, and the mixture was stirred for 35 minutes . To the reaction mixture was added water, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol). The obtained crude product was purified by preparative thin layer chromatography on silica gel (developing solvent: dichloromethane/methanol = 7/1) to give 3-(β-D-glucopyranosyloxy)-5-methyl-1-isopropyl-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole (45 mg).
$^1$H-NMR ($CD_3OD$) δ ppm:
0.50-0.65 (2H, m), 0.80-0.95 (2H, m), 1.36 (3H, d, J=6.6Hz), 1.37 (3H, d, J=6.6Hz), 1.75-1.90 (1H, m), 2.07 (3H, s), 3.15-3.50 (4H, m), 3.60-3.85 (4H, m), 4.30-4.50 (1H, m), 4.95-5.10 (1H, m), 6.85-7.10 (4H, m)

Example 29

3-(β-D-Glucopyranosyloxy)-4-{[4-(4-hydroxyphenyl)phenyl]-methyl}-5-methyl-1*H*-pyrazole

**[0123]** The title compound was prepared in a similar manner to that described in Example 21 using 4-{[4-(4-hydroxyphenyl)-phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
$^1$H-NMR ($CD_3OD$) δ ppm:
2.09 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10 (1H, m), 6.75-6.85 (2H, m), 7.15-7.25 (2H, m), 7.30-7.45 (4H, m)

Example 30

4-{[4-(3-Fluorophenyl)phenyl]methyl}-3-(β-D-Glucopyranosyloxy)-5-methyl-1*H*-pyrazole

**[0124]** The title compound was prepared in a similar manner to that described in Example 21 using 4-{[4-(3-fluorophenyl)-phenyl]methyl}-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 5-methyl-4-[(4-cyclopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy) 1*H*-pyrazole.
$^1$H-NMR ($CD_3OD$) δ ppm:
2.10 (3H, s), 3.25-3.55 (4H, m), 3.60-3.90 (4H, m), 5.00-5.15 (1H, m), 6.95-7.10 (1H, m) , 7.25-7.35 (3H, m) , 7.35-7.45 (2H, m), 7.45-7.55 (2H, m)

Example 31

3-(β-D-Glucopyranosyloxy)-5-methyl-4-{[4-(pyridin-2-yl)-phenyl]methyl}-1*H*-pyrazole

**[0125]** 5-Methyl-4-{[4-(pyridin-2-yl)phenyl]methyl}-3-(2,3,4, 6-tetraacetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole was prepared in a similar manner to that described in Example 4 using 5-methyl-4-{[4-(pyridin-2-yl)phenyl]methyl}-1,2-dihydro-3*H*-pyrazol-3-one instead of 5-methyl-4-[(4-cyclopropylphenyl)-methyl]-1,2-dihydro-3*H*-pyrazol-3-one. Then the title compound was prepared in a similar manner to that described in Example 21 using 5-methyl-4-{[4-(pyridin-2-yl) phenyl]-methyl}-3-(2,3,4,6-tetraacetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 5-methyl-4-[(4-cyclopropylphe-

nyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
$^1$H-NMR ($CD_3OD$) δ ppm:
2.10 (3H, s), 3.30-3.45 (4H, m), 3.60-3.90 (4H, m) , 5.00-5.15 (1H, m), 7.25-7.40 (3H, m), 7.75-7.95 (4H, m), 8.50-8.60 (1H, m)

Example 32

3-(β-D-Glucopyranosyloxy)-5-methyl-1-(cyclopropylmethyl)-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole

**[0126]** The title compound was prepared in a similar manner to that described in Example 28 using (bromomethyl) cyclopropane instead of 2-iodopropane.
$^1$H-NMR ($CD_3OD$) δ ppm:
0.25-0.40 (2H, m), 0.45-0.65 (4H, m) , 0.80-0.95 (2H, m), 1.05-1.25 (1H, m), 1.75-1.90 (1H, m), 2.08 (3H, s), 3.25-3.45 (4H, m), 3.55-3.90 (6H, m), 5.00-5.10 (1H, m), 6.85-7.10 (4H, m)

Example 33

3-(β-D-Glucopyranosyloxy)-1-(2-hydroxyethyl)-5-methyl-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole

**[0127]** To a suspension of 3-(β-D-glucopyranosyloxy)-5-methyl-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole (33mg) and cesium carbonate (138 mg) in N,N-dimethylformamide (1 mL) was added 2-bromoethyl acetate (0.035 mL) at 40°C, and the mixture was stirred for 2 hours. To the reaction mixture was added water, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol). The obtained crude product was dissolved in methanol (1 mL), and to the solution was added 2 mol/L aqueous sodium hydroxide solution (0.04 mL), and the mixture was stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on ODS (developing solvent: methanol/water 3/2) to give 3-(B-D-glucopyranosyloxy)-1-(2-hydroxyethyl)-5-methyl-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole (8 mg).
$^1$H-NMR ($CD_3OD$) δ ppm:
0.45-0.55 (2H, m), 0.70-0.85 (2H, m), 1.65-1.80 (1H, m), 2.01 (3H, s), 3.15-3.35 (4H, m), 3.50-3.65 (3H, m), 3.65-3.75 (3H, m), 3.90 (2H, t, J=5.5Hz), 4.95-5.05 (1H, m), 6.80-6.90 (2H, m), 6.90-7.00 (2H, m)

Example 34

3-(β-D-Glucopyranosyloxy)-5-methyl-1-cyclopentyl-4-[(4-cyclopropylphenyl)methyl]-1*H*-pyrazole

**[0128]** The title compound was prepared in a similar manner to that described in Example 28 using bromocyclopentane instead of 2-iodopropane.
$^1$H-NMR ($CD_3OD$) δ ppm:
0.55-0.65 (2H, m), 0.80-1.00 (2H, m), 1.50-1.75 (2H, m), 1.75-2.10 (7H, m), 2.07 (3H, s), 3.15-3.45 (4H, m), 3.55-3.85 (4H, m), 4.45-4.65 (1H, m) , 5.00-5.10 (1H, m), 6.85-7.10 (4H, m)

Reference Example 16

4-[(4-Ethylphenyl)methyl]-5-methyl-1,2-dihdro-3*H*-pyrazol-3-one

**[0129]** To a solution of 4-ethylbenzyl alcohol (2.5 g) and triethylamine (2.5 mL) in tetrahydrofuran (35 mL) was added methanesulfonyl chloride (1.4 mL), and the mixture was stirred at room temperature for 1 hour. Insoluble materials were removed by filtration. A solution of the obtained 4-ethylbenzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride (60%, 0.72 g) and methyl acetoacetate (1.9 mL) in 1,2-dimethoxyethane (40 mL), and the mixture was stirred at 70°C for 2 hours. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. To a solutidn of the residue in toluene (50 mL) was added hydrazine monohydrate (2.7 mL), and the mixture was stirred at 80°C for 2 hours. After the reaction mixture was cooled to room temperature, hexane was added to the mixture. The precipitates were collected by filtration, washed with water and hexane, and dried under reduced pressure to give 4-[(4-ethylphenyl)methyl]-5-methyl-1,2-dihdro-3*H*-pyrazol-3-one (1.2 g).
$^1$H-NMR (DMSO-$d_6$) δ ppm:
1.13 (3H, t, J=7.6Hz), 2.00 (3H, s), 2.45-2.60 (2H, m), 3.49 (2H, s), 7.00-7.15 (4H, m)

Reference Example 17

4-[(4-Ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0130]** To a suspension of 4-[(4-ethylphenyl)methyl]-5-methyl-1,2-dihdro-3*H*-pyrazol-3-one (0.65 g) and acetobromo-α-D-glucose (1.2 g) in tetrahydrofuran (15 mL) was added silver carbonate (0.839), and the mixture was stirred at 60°C overnight under light shielding. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran), and successively by column chromatography on silica gel (eluent: hexane/ethyl acetate = = 1/3) to give 4-[(4-ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.61 g).
$^1$H-NMR ($CDCl_3$) δ ppm:
1.19 (3H, t, J=7.6Hz). 1.86 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.12 (3H, s). 2.58 (2H, q, J=7.6Hz), 3.56 (1H. d, J=15.7Hz), 3.63 (1H, d, J=15.7Hz), 3.80-3.90 (1H, m), 4.13 (1H, dd, 3=2.4, 12.5Hz), 4.31 (1H, dd, J=4.1, 12.5Hz), 5.10-5.35 ( 3H, m), 5.50-5.65 (1H, m), 7.00-7.15 (4H, m), 8.91 (1H, brs)

Reference Example 18

1-(2-Benzyloxyethyl)-4-[(4-ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

**[0131]** To a suspension of 4-[(4-ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.0309) and cesium carbonate (0.091 g) in acetonitrile (0.4 mL) was added benzyl(2-bromoethyl)ether (0.035 mL), and the mixture was stirred at 80°C for 30 minutes. After cooling to room temperature, the reaction mixture was further stirred overnight. To the reaction mixture were added methanol (0.4 mL) and 2 mol/L aqueous sodium hydroxide solution (0.55 mL), and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, and the mixture was purified by CBA solid phase extraction (washing solvent: distilled water, eluent: methanol), and successively by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1 - 5/1) to give to give 1-(2-benzyloxyethyl)-4-[(4-ethylphenyl)-methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole (0.012 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.17 (3H, t, J=7.6Hz), 2.08 (3H, s), 2.56 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.60-3.90 (6H, m), 4.05-4.20 (2H, m), 4.30-4.45 (2H, m), 5.00-5.10 (1H, m), 7.00-7.30 (9H, m)

Reference Example 19

5-Methyl-4-[(4-methylthiophenyl)methyl]-1,2-dihdro-3*H*-pyrazol-3-one

**[0132]** The title compound was prepared in a similar manner to that described in Reference Example 16 using 4-methylthiobenzyl alcohol instead of 4-ethylbenzyl alcohol.
$^1$H-NMR (DMSO-$d_6$) δ ppm:
1.99 (3H, s), 2.42 (3H, s), 3.50 (2H, s), 7.05-7.20 (4H, m)

Reference Example 20

5-Methyl-4-[(methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0133]** The title compound was prepared in a similar manner to that described in Reference Example 17 using 5-methyl-4-[(4-methylthiophenyl)methyl]-1,2-dihdro-3*H*-pyrazol-3-one instead of 4-[(4-ethylphenyl)methyl]-5-methyl-1,2-dihdro-3*H*-pyrazol-3-one.
$^1$H-NMR ($CDCl_3$) δ ppm:
1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.12 (3H, s), 2.44 (3H, s), 3.50-3.65 (2H, m), 3.80-3.90 (1H. m), 4.13 (1H, dd, J=2.4, 12.4Hz), 4.31 (1H, dd, J=4.1, 12.4Hz), 5.15-5.30 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m), 8.65-8.85 (1H, brs)

Reference Example 21

3-(β-D-Glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)-methyl]-1*H*-pyrazole

**[0134]** To a solution of 5-methyl-4-[(methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.42 g) in ethanol (5 mL) was added sodium methoxide (28% methanol solution, 0.042 mL). and the mixture

was stirred at room temperature for 1 hour. The reaction mixture was concentratedunderreducedpressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 5/1) to give 3-(β-D-glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)methyl]-1*H*-pyrazole (0.23 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
2.06 (3H, s), 2.42 (3H, s), 3.20-3.45 (4H, m), 3.55-3.75 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 7.05-7.20 (4H, m)

Reference Example 22

4-[(4-Isopropoxyphenyl)methyl]-5-methyl-1,2-dihdro-3*H*-pyrazol-3-one

**[0135]** To a solution of 4-isopropoxybenzyl alcohol (0.34 g) in tetrahydrofuran (6 mL) were added triethylamine (0.28 mL) and methanesulfonyl chloride (0.16 mL), and the mixture was stirred at room temperature for 30 minutes. Insoluble materials were removed by filtration. A solution of the obtained 4-isopropoxybenzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride (60%, 81 mg) and methyl acetoacetate (0.20 mL) in 1,2-dimethoxyethane (10 mL), and the mixture was stirred at 80°C overnight. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (5 mL). To the mixture was added anhydrous hydrazine (0.19 mL), and the mixture was stirred at 80°C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 4-[(4-isopropoxyphenyl) methyl]-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (95 mg).
$^1$H-NMR (DMSO-$d_6$) δ ppm:
1.22 (6H, d, J=6.0Hz), 1.99 (3H, s), 3.45 (2H, s), 4.40-4.60 (1H, m), 6.65-6.80 (2H, m), 6.95-7.10 (2H, m)

Reference Example 23

4-[(4-Isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0136]** To a suspension of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (46 mg), acetobromo-α-D-glucose (99 mg) and 4A molecular sieves in tetrahydrofuran (3 mL) was added silver carbonate (66 mg), and the mixture was stirred at 65°C overnight under light shielding. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran), and successively by preparative thin layer chromatography on silica gel (developing solvent: ethyl acetate/hexane = 2/1) to give 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (42 mg).
$^1$H-NMR ($CDCl_3$) δ ppm:
1.25-1.35 (6H, m), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.45-3.65 (2H, m), 3.80-3.90 (1H. m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 4.40-4.55 (1H, m), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.05 (2H, m)

Reference Example 24

3-(β-D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl)-5-methyl-1*H*-pyrazole

**[0137]** To a solution of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (61 mg) in ethanol (3 mL) was added 1 mol/L aqueous sodium hydroxide solution (0.53 mL), and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, and the residue was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol) to give 3-(β-D-glucopyranosyl-oxy)-4-[ (4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (39 mg).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.26 (6H, d, J=5.9Hz), 2.05 (3H, 5), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.90 (1H, m), 4.45-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

Example 35

4-((4-Ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole

**[0138]** To a solution of 1-(2-benzyloxyethyl)-4-[(4-ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole (0.012 g) in ethanol (2 mL ) was added a catalytic amount of 10% palladium-carbon powder, and the mixture was

stirred at room temperature under a hydrogen atmosphere for 30 minutes. Insoluble materials were removed by filtration, and the solvent was removed under reduced pressure to give 4-[(4-ethylphenyl)-methyl]-3-(β-D-glucopyranosyloxy)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole (0.011 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.18 (3H, t, J=7.6Hz). 2.11 (3H, s), 2.56 (2H, q, J=7.6Hz), 3.25-3.50 (4H, m), 3.55-3.95 (6H, m), 3.95-4.05 (2H, m), 5.05-5.15 (1H, m), 7.00-7.15 (4H, m)

Example 36

3-(β-D-Glucopyranosyloxy)-1-(3-hydroxypropyl)-5-methyl-4-[(4-methylthiophenyl)methyl] -1*H*-pyrazole

**[0139]** To a suspension of 3-(β-D-glucopyranosyloxy)-5-methyl-4-[ (4-methylthiophenyl) methyl]-1*H*-pyrazole (0.020 g) and cesium carbonate (0.11 g) in *N,N*-dimethylformamide (0.5ML) was added 3-bromopropanol (0.022 mL), and the mixture was stirred at 40°C overnight. To the reaction mixture was added water, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol), and successively by column chromatography on silica gel (eluent: dichloromethane/methanol = 5/1) to give 3-(β-D-glucopyranosyloxy)-1-(3-hydroxypropyl)-5-methyl-4-[(4-methylthiophenyl)methyl]-1*H*-pyrazole (0.011 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.85-1.95 (2H, m), 2.10 (3H, s), 2.42 (3H, s), 3.25-3.45 (4H, m) , 3.45-3.55 (2H, m), 3.60-3.75 (3H, m), 3.82 (1H, dd, J=1.8, 12.2Hz), 3.95-4.10 (2H, m), 5.00-5.15 (1H,m); 7.05-7.20 (4H, m)

Example 37

1-Allyl-4-[(4-ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

**[0140]** To a suspension of 4-[(4-ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.030 g) and cesium carbonate (0.036 g) in acetonitrile (0.4 mL) was added allyl iodide (0.010 mL), and the mixture was stirred at room temperature for 1 hour. To the reaction mixture were added methanol (0.4 mL) and 1 mol/L aqueous sodium hydroxide solution (0.5 mL), and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol), and successively by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1-allyl-4-[(4-ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole (0.018 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.18 (3H, t, J=7.5Hz), 2.04 (3H, s), 2.57 (2H, q, J=7.5Hz), 3.25-3.45 (4H, m), 3.55-3.95 (4H, m), 4.50-4.65 (2H, m), 4.80-4.95 (1H, m), 5.00-5.20 (2H, m), 5.85-6.00 (1H, m), 7.00-7.15 (4H, m)

Example 38

1-(Cyclopropylmethyl)-3-(β-D-glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)methyl]-1*H*-pyrazole

**[0141]** To a solution of 3-(β-D-glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)methyl]-1*H*-pyrazole (0.081 g) in *N,N*-dimethylformamide (1 mL) were added cesium carbonate (0.40 g), bromomethylcyclopropane (0.099 mL) and a catalytic amount of sodium iodide, and the mixture was stirred at room temperature for 7 days. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1 - 8/1) to give 1-(cyclopropylmethyl)-3-(β-D-glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)methyl]-1*H*-pyrazole (0.041 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
0.25-0.40 (2H, m), 0.40-0.60 (2H, m), 1.05-1.25 (1H, m), 2.10 (3H, s), 2.42 (3H, s), 3.25-3.45 (4H, m), 3.55-3.90 (6H, m), 5.00-5.10 (1H, m), 7.00-7.25 (4H, m)

Example 39

4-[(4-Ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-1-(3-hydroxypropyl) -5-methyl-1*H*-pyrazole

**[0142]** To a suspension of 4-[(4-ethylphenyl) methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.030 g) and cesium carbonate (0.091 g) in acetonitrile (0.4 mL) was added benzyl(3-bromopropyl)ether (0.039 mL), and the mixture was stirred at 80°C for 30 minutes. To the reaction mixture were added methanol (0.4 mL)

and 2 mol/L aqueous sodium hydroxide solution (0.55 mL), and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol). To the resulting eluent was added a catalytic amount of 10% palladium-carbon powder, and the mixture was stirred at room temperature under a hydrogen atmosphere for 3 days. Insoluble materials were removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by liquid chromatography on ODS (eluent: methanol/water = 40/60) to give 4-[(4-ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-1-(3-hydroxypropyl)-5-methyl-1*H*-pyrazole (0.0080 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.18 (3H, t, J=7.5Hz), 1.85-2.00 (2H, m), 2.10 (3H, s), 2.57 (2H, q, J=7.5Hz), 3.25-3.45 (4H, m) , 3.45-3.55 (2H, m) , 3.55-3.90 (4H, m), 3.95-4.10 (2H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

Example 40

1-(Cyclopropylmethyl)-3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl-5-methyl-1*H*-pyrazole

**[0143]** To a suspension of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (0.050 g), cesium carbonate (0.209) and a catalytic amount of sodium iodide in *N,N*-dimethylformamide (1 mL) was added bromomethylcyclopropane (0.050 g) at 50°C, and the mixture was stirred for 3 days. Water was added to the reaction mixture, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol), and successively by column chromatography on silica gel (eluent: dichloromethane/methanol = 8/1) to give 1-(cyclopropylmethyl)-3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (0.034 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
0.25-0.35 (2H, m), 0.45-0.55 (2H, m), 1.10-1.25 (1H, m), 1.26 (6H, d, J=6.1Hz), 2.09 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.90 (3H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

Example 41

1-Cyclopentyl-3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole

**[0144]** To a suspension of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (0.050 g) and cesium carbonate (0.20 g) in *N,N*-dimethylformamide (1 mL) was added cyclopentyl bromide (0.055 g) at 80°C, and the mixture was stirred for 30 minutes. After cooling to room temperature, water was added to the reaction mixture, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol), and successively by column chromatography on silica gel (eluent: dichloromethane/methanol = 8/1) to give 1-cyclopentyl-3-(B-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (0.034 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
1.26 (6H, d, J=6.1Hz), 1.55-1.75 (2H, m), 1.80-2.05 (6H, m), 2.03 (3H, s), 3.15-3.30 (1H, m), 3.30-3.45 (3H, m), 3,60-3.75 (3H, m), 3.77 (1H, dd, J=2.6, 12.0Hz), 4.40-4.65 (2H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

Example 42

1-(Cyclopropylmethyl)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(6-*O*-propionyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

**[0145]** To a solution of 1-(cyclopropylmethyl)-3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (0.409) in 2,4,6-trimethylpyridine (1.5 mL ) was added propionyl chloride (0.0088 g)at 0°C, and the mixture was stirred for 3 hours. Citric acid monohydrate (3.3 g) and water were added to the reaction mixture, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol), and successively by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1-(Cyclopropylmethyl)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(6-*O*-propionyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (0.20 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
0.25-0.35 (2H, m), 0.45-0.55 (2H, m), 1.05 (3H, t, J=7.6Hz), 1.15-1.25 (1H, m), 1.26 (6H, d, J=6.3Hz), 2.07 (3H, s), 2.29 (2H, q, J=7.6Hz), 3.30-3.55 (4H, m), 3.55-3.70 (2H, m), 3.82 (2H, d, J=6.7Hz), 4:22 (1H, dd, J=5.4, 12.0Hz), 4.32 (1H, dd, J=2.3, 12.0Hz), 4.45-4.55 (1H, m), 5.05-5.15 (1H, m) , 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

Example 43

1-(Cyclopropylmethyl)-3-(6-*O*-ethoxycarbonyl-β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole

**[0146]** To a solution of 1-(cyclopropylmethyl)-3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (0.050 g) in 2,4,6-trimethylpyridine (1 mL) was added ethyl chloroformate (0.035 g), and the mixture was stirred at room temperature overnight. Citric acid monohydrate (3.3 g) and water were added to the reaction mixture, and the mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol), and successively by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1-(cyclopropylmethyl)-3-(6-*O*-ethoxycarbonyl-β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (0.043 g).
$^1$H-NMR ($CD_3OD$) δ ppm:
0.25-0.35 (2H, m) , 0.45-0.55 (2H, m), 1.05-1.25 (1H, m), 1.23 (3H, t, J=7.1Hz), 1.26 (6H, d, J=6.1Hz), 2.08(3H, s), 3.30-3.50 (4H, m). 3.62 (1H, d, J=16.2Hz), 3.67 (1H, d, J=16.2Hz), 3.82 (2H, d, J=6.6Hz). 4.13 (2H, q, J=7.1Hz), 4.23 (1H, dd, J=5.2, 11.7Hz), 4.37 (1H, dd, J=2.1. 11.7Hz), 4.45-4.55 (1H. m), 5.05-5.15 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

Test Example 1

Assay for inhibitory effect on human SGLT2 activity

1) Construction of the plasmid vector expressing human SGLT2

**[0147]** Preparation of the cDNA library for PCR amplification was performed by reverse transcription of a total RNA deprived from human kidney (Ori gene) with oligo dT as the primer, using SUPERSCRIPT Preamplification System (Gibco-BRL: LIFE TECHNOLOGIES). The DNA fragment coding for human SGLT2 was amplified by the PCR reaction, in which the human kidney cDNA library described above was used as the template and the following oligo nucleotides 0702F and 0712R, presented as Sequence Numbers 1 and 2 respectively, were used as the primers. The amplified DNA fragment was ligated into pCR-Blunt (Invitrogen), a vector for cloning, according to standard method of the kit. The *Escherichia coli* HB101 was transformed according to usual method and then selection of the transformants was performed on the LB agar medium containing 50 μg/mL of kanamycin. After plasmid DNA was extracted and purified from the one of the transformants, amplifying of the DNA fragment coding for human SGLT2 was performed by the PCR reaction, in which the following oligo nucleotides 0714F and 0715R, presented as Sequence Numbers 3 and 4 respectively, were used as the primers. The amplified DNA fragment was digested with restriction enzymes, Xho I and Hind III, and then purified with Wizard Purification System (Promega). This purified DNA fragment was inserted at the corresponding restriction sites of pcDNA3.1 (-) Myc/His - B (Invitrogen), a vector for expressing of fusion protein. The *Escherichia coil* HB101 was transformed according to usual method and then selection of the transformant was performed on the LB agar medium containing 100 μg/mL of ampicillin. After plasmid DNA was extracted and purified from this transformant, the base sequence of the DNA fragment inserted at the multi-cloning sites of the vector pcDNA3.1 ( - ) Myc/His - B was analyzed. This clone had a single base substitution (ATC which codes for the isoleucine-433 was substituted by GTC) compared with the human SGLT2 reported by Wells *et al* (Am. J. Physiol., Vol. 263, pp. 459-465 (1992)). Sequentially, a clone in which valine is substituted for isoleucine-433 was obtained. This plasmid vector expressing human SGLT2 in which the peptide presented as Sequence Number 5 is fused to the carboxyl terminal alanine residue was designated KL29.

Sequence Number 1 ATGGAGGAGCACACAGAGGC
Sequence Number 2 GGCATAGAAGCCCCAGAGGA
Sequence Number 3 AACCTCGAGATGGAGGAGCACACAGAGGC
Sequence Number 4 AACAAGCTTGGCATAGAAGCCCCAGAGGA
Sequence Number 5 KLGPEQKLISEEDLNSAVDHHHHHH

2) Preparation of the cells expressing transiently human SGLT2

**[0148]** KL29 , the plasmid coding human SGLT2 , was transfected into COS-7 cells (RIKEN CELL BANK RCB0539) by electroporation. Electroporation was performed with GENE PULSER II (Bio-Rad Laboratories) under the condition: 0.290 kV, 975 μF, 2 x $10^6$ cells of COS-7 cell and 20 μg of KL29 in 500 μL of OPTI-MEM I medium (Gibco-BRL: LIFE TECHNOLOGIES) in the 0.4 cm type cuvette. After the gene transfer, the cells were harvested by centrifugation and

resuspended with OPTI-MEM I medium (1mL/cuvette). To each well in 96-wells plate, 125 μL of this cell suspension was added. After overnight culture at 37 °C under 5 % $CO_2$, 125 μL of DMEM medium which is containing 10 % of fetal bovine serum (Sanko Jyunyaku), 100 units/mL sodium penicillin G (Gibco-BRL: LIFE TECHNOLOGIES), and 100 μg/mL streptomycin sulfate (Gibco-BRL: LIFE TECHNOLOGIES) was added to each well. These cells were cultured until the next day and then they were used for the measurement of the inhibitory activity against the uptake of methyl-α-D-glucopyranoside.

3) Measurement of the inhibitory activity against the uptake of methyl-α-D-glucopyranoside

**[0149]** After a test compound was dissolved in dimethyl sulfoxide and diluted with the uptake buffer (a pH 7.4 buffer containing 140 mM sodium chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 5 mM methyl-α-D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane), each diluent was used as test sample for measurement of the inhibitory activity. After removal of the medium of the COS-7 cells expressing transiently human SGLT2, to each well 200 μL of the pretreatment buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)-aminomethane) was added, and the cells were incubated at 37°C for 10 minutes. After the pretreatment buffer was removed, 200 μL of the same buffer was added again, and the cells were incubated at 37 °C for 10 minutes . The buffer for measurement was prepared by adding and mixing 7 μL of methyl-α-D-(U-14C)glucopyranoside (Amersham pharmacia Biotech) to 525μL of the prepared test sample. For the control, the buffer for measurement without any test compound was prepared. For estimate of the basal uptake in the absence of a test compound and sodium, the buffer for measurement of the basal uptake, which contains 140 mM choline chloride in place of sodium chloride, was prepared similarly. After the pretreatment buffer was removed, 75 μL of the each buffer for measurement was added to each well, and the cells were incubated at 37 °C for 2 hours. After the buffer for measurement was removed, 200 μL of the washing buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM methyl-α-D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane) was added to each well and immediately removed. After two additional washing, the cells were solubilized by addition of 75 μL of 0.2 mol/L aqueous sodium hydroxide solution to each well. After the cell lysates were transferred to the PicoPlate (Packard) and 150 μL of MicroScint-40 (Packard) was added to each well, the radioactivity was measured with microplate scintillation counter TopCount (Packard). The difference in uptake was obtained as 100% value by subtracting the radioactivity in the basal uptake from that in control and then the concentrations at which 50% of uptake were inhibited ($IC_{50}$) were calculated from the concentration-inhibition curve by least square method. The results are shown in the following Table 1.

[Table 1]

| Test compound | $IC_{50}$ value (nM) |
|---|---|
| Example 20 | 15 |
| Example'21 | 18 |
| Example 22 | 41 |
| Example 23 | 46 |
| Example 24 | 57 |
| Example 25 | 65 |
| Example 26 | 150 |
| Example 27 | 210 |
| Example 32 | 26 |
| Example 38 | 45 |
| Example 39 | 47 |
| WAY-123783 | >100000 |

**Industrial Applicability**

**[0150]** The glucopyranosyloxyboyrazole derivatives represented by the above general formula (I) of the present

invention, pharmaceutically acceptable salts thereof and prodrugs thereof show an excellent hypoglycemic effect by excreting excess glucose into the urine through preventing the reabsorption of glucose at the kidney because they exhibit an excellent inhibitory activity in human SGLT2 . The present invention can provide drugs for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications, obesity or the like. In addition, since compounds represented by the above general formula (III) or (IV) or salts thereof are important as intermediates in the production of the compounds represented by the above general formula (I), pharmaceutically acceptable salts thereof and prodrugs thereof, the compounds represented by the above general formula (I), pharmaceutically acceptable salts thereof and prodrugs thereof of the present invention can be readily prepared via such compounds.

[SEQUENCE LISTING FREE TEXT]

**[0151]**

Sequence Number 1: Synthetic DNA primer
Sequence Number 2: Synthetic DNA primer
Sequence Number 3: Synthetic DNA primer
Sequence Number 4: Synthetic DNA primer
Sequence Number 5: Peptide fused to the carboxyl terminal alanine residue of human SGLT2

SEQUENCE LISTING

<110> KISSEI PHARMACEUTICAL CO., LTD.
NISHIMURA, Toshihiro
FUSHIMI, Nobuhiko
FUJIKURA, Hideki
KATSUNO, Kenji
KOMATSU, Yoshimitsu
ISAJI, Masayuki

<120> GLUCOPYRANOSYLOXYPYRAZOLE DERIVATIVES AND PHARMACEUTICAL USES THEREOF

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<223> Peptide fused to the carboxyl terminal alanine
residue of human SGLT2

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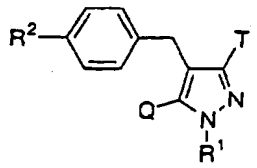
1 5 10 15

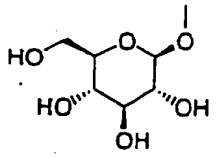
Ala Val Asp His His His His His His
20 25

## Claims

1. A glucopyranosyloxypyrazole derivative represented by the general formula:



wherein one of Q and T represents a group represented by the general formula:

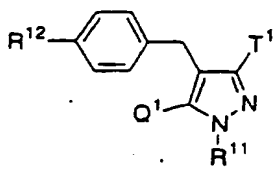


while the other represents a lower alkyl group or a halo(lower alkyl) group; $R^1$ represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group or a group represented by the general formula: HO-$A^1$- wherein $A^1$ represents a lower alkylene group; $R^2$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: HO-$A^2$- wherein $A^2$ represents a lower alkylene group; and with the proviso that $R^2$ does not represent either a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl)group or a halogen atom when $R^1$ represents a hydrogen atom or a lower alkyl group, a pharmaceutically acceptable salt thereof or a prodrug thereof.

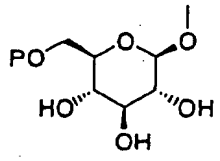
2. A glucopyranosyloxypyrazole derivative as claimed in claim 1 wherein $R^2$ represents a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: HO-$A^2$- wherein $A^2$ represents a lower alkylene group, a pharmaceutically acceptable salt thereof or a prodrug thereof.

3. A glucopyranosyloxypyrazole derivative as claimed in claim 1 wherein $R^1$ represents a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted ( lower alkyl ) group or a group represented by the general formula: HO-$A^1$- wherein $A^1$ represents a lower alkylene group; $R^2$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, a pharmaceutically acceptable salt thereof or a prodrug thereof.

4. A glucopyranosyloxypyrazole derivative represented by



the general formula:
wherein one of $Q^1$ and $T^1$ represents a group represented by the general formula:

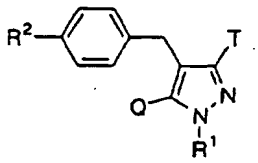


wherein P represents a hydrogen atom or a group forming prodrug; the other represents a lower alkyl group or a halo(lower alkyl) group; $R^{11}$ represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group, a group forming prodrug or a group represented by the general formula: $P^1$-O-$A^1$- wherein $P^1$ represents a hydrogen atom or a group forming prodrug; and $A^1$ represents a lower alkylene group; $R^{12}$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^2$-O-$A^2$- wherein $P^2$ represents a hydrogen atom or a group forming prodrug; and $A^2$ represents a lower alkylene group; and with the proviso that $R^{12}$ does not represent either a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl)group or a halogen atom when at least one of P, $R^{11}$ and $R^{12}$ has a group forming prodrug and $R^{11}$ represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof.

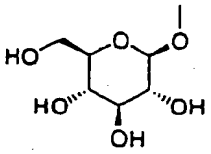
5. A glucopyranosyloxypyrazole derivative as claimed in claim 4 wherein $R^{12}$ represents a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from ahalogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^2$-O-$A^2$- wherein $P^2$ represents a hydrogen atom or a group forming prodrug; and $A^2$ represents a lower alkylene group; or a pharmaceutically acceptable salt thereof.

6. A glucopyranosyloxypyrazole derivative as claimed in claim 4 wherein $R^{11}$ represents a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group, a group forming prodrug or a group represented by the general formula: $P^1$-O-$A^1$- wherein $P^1$ represents a hydrogen atom or a group forming prodrug; and $A^1$ represents a lower alkylene group; $R^{12}$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, or a pharmaceutically acceptable salt thereof.

7. A glucopyranosyloxypyrazole derivative as claimed in claim 4, represented by the general formula:



wherein one of Q and T represents a group represented by the general formula:



while the other represents a lower alkyl group or a halo(lower alkyl) group; $R^1$ represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group or a group represented by the general formula: HO-$A^1$- wherein $A^1$ represents a lower alkylene group; $R^2$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: HO-$A^2$- wherein $A^2$ represents a lower alkylene group; and with the proviso that $R^2$ does not represent either a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo ( lower alkyl) group or a halogen atom when $R^1$ represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof.

**8.** A glucopyranosyloxypyrazole derivative as claimed in claim 7 wherein $R^2$ represents a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: HO-$A^2$- wherein $A^2$ represents a lower alkylene group, or a pharmaceutically acceptable salt thereof.

**9.** A glucopyranosyloxypyrazole derivative as claimed in claim 7 wherein $R^1$ represents a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group or a group represented by the general formula: HO-$A^1$- wherein $A^1$ represents a lower alkylene group; $R^2$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, or a pharmaceutically acceptable salt thereof.

**10.** A glucopyranosyloxypyrazole derivative as claimed in any one of claims 4-6 wherein at least one of P, $R^{11}$ or $R^{12}$ has a group forming prodrug, or a pharmaceutically acceptable salt thereof.

**11.** A glucopyranosyloxypyrazole derivative as claimed in claim 10 wherein each group forming prodrug in P, $P^1$ and $P^2$ is a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group or a lower alkoxy-substituted (lower alokoxycarbonyl) group, and a group forming prodrug in $R^{11}$ excluding $P^1$ is a lower acyl group, a lower alkoxycarbonyl group, a lower acyloxymethyl group or a lower alkoxycarbonyloxymethyl group, or a pharmaceutically acceptable salt thereof.

**12.** A pharmaceutical composition comprising as an active ingredient a glucopyranosyloxypyrazole derivative as claimed in any one of claims 1-11, a pharmaceutically acceptable salt thereof or a prodrug thereof.

**13.** A pharmaceutical composition as claimed in claim 12 wherein the composition is a human SGLT2 inhibitor.

**14.** A pharmaceutical composition as claimed in claim 12 or 13 wherein the composition is a drug for the prevention or treatment of a disease associated with hyperglycemia.

**15.** A pharmaceutical composition as claimed in claim 14 wherein the disease associated with hyperglycemia is selected from the group consisting of diabetes, diabetic complications, obesity, hyperinsulinemia, glucose metabolism disorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia and gout.

**16.** A pharmaceutical composition as claimed in claim 15 wherein the disease associated with hyperglycemia is diabetes.

**17.** A pharmaceutical composition as claimed in claim 15 wherein the disease associated with hyperglycemia is diabetic complications.

**18.** A pharmaceutical composition as claimed in claim 15 wherein the disease associated with hyperglycemia is obesity.

**19.** A method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of a glucopyranosyloxypyrazole derivative as claimed in any one of claims 1-11, a

pharmaceutically acceptable salt thereof or a prodrug thereof.

20. A use of a glucopyranosyloxypyrazole derivative as claimed in any one of claims 1-11, a pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

21. A pharmaceutical combination which comprises (A) a glucopyranosyloxypyrazole derivative claimed in any one of claims 1-11, a pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethylglutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a $\beta_3$-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an $\alpha_2$-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

22. A pharmaceutical combination claimed in claim 21 for the prevention or treatment of a disease associated with hyperglycemia.

23. A pharmaceutical combination claimed in claim 22 wherein a component (B) is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist and an appetite suppressant, and the disease associated with hyperglycemia is diabetes.

24. A pharmaceutical combination claimed in claim 23 wherein a component (B) is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue and an amylin agonist.

25. A pharmaceutical combination claimed in claim 24 wherein a component (B) is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer and an insulin preparation.

26. A pharmaceutical combination claimed in claim 22 wherein a component (B) is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin se-

cretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, glycogen synthase kinase-3 inhibitors, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, anN-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, aplatelet derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist and a diuretic agent, and the disease associated with hyperglycemia is diabetic complications.

**27.** A pharmaceutical combination claimed in claim 26 wherein a component (B) is at least one member selected from the group consisting of an aldose reductase inhibitor, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor and an angiotensin II receptor antagonist.

**28.** A pharmaceutical combination claimed in claim 22 wherein a component (B) is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, a $\beta_3$-adrenoceptor agonist and an appetite suppressant, and the disease associated with hyperglycemia is obesity.

**29.** A pharmaceutical combination claimed in claim 28 wherein a component (B) is at least one member selected from the group consisting of a $\beta_3$-adrenoceptor agonist and an appetite suppressant.

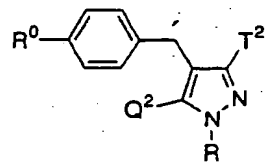
**30.** A pharmaceutical combination claimed in claim 29 wherein the appetite suppressant is a drug selected from the group consisting of a monoamine reuptake inhibitor, a serotonin reuptake inhibitor, a serotonin releasing stimulant, a serotonin agonist, a noradrenaline reuptake inhibitor, a noradrenaline releasing stimulant, an $\alpha_1$-adrenoceptor agonist, a $\beta_2$-adrenoceptor agonist, a dopamine agonist, a cannabinoid receptor antagonist, a γ-aminobutyric acid receptor antagonist, a $H_3$-histamine antagonist, L-histidine, leptin, a leptin analogue, a leptin receptor agonist, a melanocortin receptor agonist, α-melanocyte stimulating hormone, cocaine-and amphetamine-regulated transcript, mahogany protein, an enterostatin agonist, calcitonin, calcitonin-gene-related peptide, bombesin, a cholecystokinin agonist, corticotropin-releasing hormone, a corticotropin-releasing hormone analogue, a corticotropin-releasing hormone agonist, urocortin, somatostatin, a somatostatin analogue, a somatostatin receptor agonist, pituitary adenylate cyclase-activating peptide, brain-derived neurotrophic factor, ciliary neurotrophic factor, thyrotropin-releasing hormone, neurotensin, sauvagine, a neuropeptide Y antagonist, an opioid peptide antagonist, a galanin antagonist, a melanin-concentrating hormone antagonist, an agouti-related protein inhibitor and an orexin receptor antagonist.

**31.** A method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of (A) a glucopyranosyloxypyrazole derivative claimed in any one of claims 1-11, a pharmaceutically acceptable salt thereof or a prodrug thereof, in combination with (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-κB inhibitor, a lipid peroxidase inhibitor, an N-acetylated-α-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal

growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a $\beta_3$-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an $\alpha_2$-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

**32.** A use of (A) a glucopyranosyloxypyrazole derivative claimed in any one of claims 1-11, a pharmaceutically acceptable salt thereof or a prodrug thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, ahepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a $\gamma$-aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF-$\kappa$B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated-$\alpha$-linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethylglutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a $\beta_3$-adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an $\alpha_2$-adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer, for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

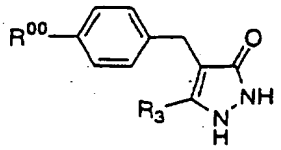
**33.** A glucopyranasyloxypyrazole derivative represented by the general formula:




wherein one of $Q^2$ and $T^2$ represents 2,3,4,6-tetra-*O*-acetyl-$\beta$-D-glucopyranosyloxy group and the other represents a lower alkyl group or a halo (lower alkyl) group; R represents a hydrogen atom, a lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkyl-substituted (lower alkyl) group or a group represented by the general formula: $P^{10}$-O-$A^1$- wherein $P^{10}$ represents a hydrogen atom or a hydroxy-protective group; and $A^1$ represents a lower alkylene group; $R^0$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group, a halogen atom, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^{20}$-O-$A^2$- wherein $P^{20}$ represents a hydrogen atom or a hydroxy-protective group; and $A^2$ represents a lower alkylene group; and with the proviso that $R^0$ does not represent either

a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl)group or a halogen atom when R represents a hydrogen atom or a lower alkyl group, or a salt thereof.

**34.** A glucopyranosyloxypyrazole derivative represented by the general formula:



wherein $R^{00}$ represents a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, a cyclic lower alkylidenemethyl group, a phenyl group which may have 1-3 different or same groups selected from a halogen atom and a hydroxy group, a 5- or 6-membered aromatic heterocyclic group which contains 1-4 different or same atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in the ring, or a group represented by the general formula: $P^{20}$-O-$A^2$- wherein $P^{20}$ represents a hydrogen atom or a hydroxy-protective group; and $A^2$ represents a lower alkylene group; and $R^3$ represents a lower alkyl group or a halo(lower alkyl) group, or a salt thereof.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/01707

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07H17/02, C07D233/70, 417/10, 401/10, A61K31/7056, 31/706, A61P43/00, 3/10, 3/04, 3/06, 9/10, 9/12, 9/04, 7/10, 19/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07H17/02, C07D233/70, 417/10, 401/10, A61K31/7056, 31/706, A61P43/00, 3/10, 3/04, 3/06, 9/10, 9/12, 9/04, 7/10, 19/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY(STN), CAPLUS(STN), CAOLD(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>A | KENNETH L. KEES, et al., New Potent Antihyperglycemic Agents in db/db Mice: Synthesis and Structure-Activity Relationship Studies of (4-Substitutedbenzyl)(trifluoromethyl) pyrazoles and -pyrazolones, J.Med.Chem., 1996, Vol.39, No.20, pages 3920 to 3928<br>Compound 22 | 34<br>1-18,20-30,32, 33 |
| X<br>A | US, 5264451, A (American Home Products Corp.), 23 November, 1993 (23.11.93),<br>Example 19<br>& US 5274111 A | 34<br>1-18,20-30,32, 33 |
| A | JP, 4-234851, A (Laboratories UPSA), 24 August, 1992 (24.08.92),<br>& EP 449699 A2 & FR 2659655 A1<br>& ZA 9101925 A & AU 9173591 A1<br>& CA 2038428 A | 1-18,20-30, 32-34 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 25 March, 2002 (25.03.02) | 09 April, 2002 (09.04.02) |
| Name and mailing address of the ISA/<br>Japanese Patent Office | Authorized officer |
| Facsimile No. | Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/01707

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP, 598359, A1 (Tanabe Seiyaku Co., Ltd.), 25 May, 1994 (25.05.94), & JP 2906978 B2 & CA 2102591 A & US 5424406 A & TW 283643 A & US 5731292 A & SG 54120 A1 & DE 69328856 E & ES 2149186 T3 & KR 211438 B1 | 1-18,20-30, 32-34 |
| P,A | WO, 01/16147, A1 (Kissei Pharmaceutical Co., Ltd.), 08 March, 2001 (08.03.01), (Family: none) | 1-18,20-30, 32-34 |

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

## INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/01707

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: 19, 31
because they relate to subject matter not required to be searched by this Authority, namely:
The inventions as set forth in claims 19 and 31 pertain to methods for treatment of the human body by therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

Printer Friendly

10/692,738 N-SUBSTITUTED PYRAZOLE-O-GLYCOSIDE DERIVATIVES AND THERAPEUTIC AGENT FOR DIABETES CONTAINING THE SAME

Patent Term Adjustment History

| Patent Term Adjustment (PTA) for Application Number: 10/692,738 | | | |
|---|---|---|---|
| | | | Days |
| Filing or 371(c) Date: | 10-27-2003 | USPTO Delay (PTO): | 44 |
| Issue Date of Patent: | 06-21-2005 | Three Years: | - |
| Pre-Issue Petitions (days): | +0 | Applicant Delay(APPL): | 48 |
| Post-Issue Petitions (days): | +0 | Total PTA: | 0 |
| USPTO Adjustment(days): | +0 | Explanation Of Calculations | |

**Patent Term Adjustment History**

| Date | Contents Description | PTO(Days) | APPL (Days) |
|---|---|---|---|
| 06-21-2005 | Patent Issue Date Used in PTA Calculation | | |
| 05-19-2005 | Receipt into Pubs | | |
| 05-18-2005 | Dispatch to FDC | | |
| 05-18-2005 | Application Is Considered Ready for Issue | | |
| 05-09-2005 | Issue Fee Payment Verified | | |
| 05-09-2005 | Issue Fee Payment Received | | |
| 05-05-2005 | Miscellaneous Incoming Letter | ⇧ | 48 |
| 03-14-2005 | Workflow - File Sent to Contractor | ⇧ | ⇧ |
| 02-09-2005 | Mail Notice of Allowance | 44 | |
| 02-08-2005 | Issue Revision Completed | ⇧ | |
| 02-08-2005 | Notice of Allowance Data Verification Completed | ⇧ | |
| 02-08-2005 | Case Docketed to Examiner in GAU | ⇧ | |
| 02-07-2005 | Notice of Allowability | ⇧ | |
| 01-25-2005 | Case Docketed to Examiner in GAU | ⇧ | |
| 01-25-2005 | Case Docketed to Examiner in GAU | ⇧ | |
| 12-09-2004 | Reference capture on IDS | ⇧ | |
| 12-09-2004 | Information Disclosure Statement (IDS) Filed | ⇧ | |
| 03-12-2004 | IFW TSS Processing by Tech Center Complete | ⇧ | |
| 03-12-2004 | Case Docketed to Examiner in GAU | ⇧ | |
| 02-23-2004 | Application Return from OIPE | ⇧ | |
| 02-23-2004 | Application Return TO OIPE | ⇧ | |
| 02-23-2004 | Application Dispatched from OIPE | ⇧ | |
| 02-23-2004 | Application Is Now Complete | ⇧ | |
| 02-09-2004 | Cleared by OIPE CSR | ⇧ | |
| 01-27-2004 | Information Disclosure Statement (IDS) Filed | ⇧ | |
| 12-27-2003 | IFW Scan & PACR Auto Security Review | ⇧ | |
| 12-19-2003 | Preliminary Amendment | ⇧ | |
| 10-27-2003 | Preliminary Amendment | ⇧ | |
| 10-27-2003 | Initial Exam Team nn | ⇧ | |

Close Window

# Clarification of 37 CFR 1.704(c)(10) - Reduction of Patent Term Adjustment for Certain Types of Papers Filed After a Notice of Allowance has been Mailed

Patent term adjustment under 35 U.S.C. 154(b)(1) is reduced by the period of time during which the applicant "failed to engage in reasonable efforts" to conclude prosecution (i.e., processing or examination of an application). See 35 U.S.C. 154(b)(2)(C)(i). Pursuant to 35 U.S.C. 154(b)(2)(C)(iii), the United States Patent and Trademark Office (Office) has prescribed regulations setting forth the circumstances constituting a failure to engage in reasonable efforts to conclude prosecution (i.e., processing or examination of an application). See 37 CFR 1.704. After a "Notice of Allowance" has been mailed, submissions by an applicant that cause a delay in processing or examination of an application will be considered a "failure to engage in reasonable efforts" to conclude prosecution. See 37 CFR 1.704(c)(10) ("failure to engage in reasonable efforts" to conclude prosecution includes submission of an amendment under 37 CFR 1.312 or other paper after a "Notice of Allowance" has been mailed). The reason such a submission is considered a "failure to engage in reasonable efforts" to conclude processing or examination of an application is that delaying the submission of such papers until after an application is allowed causes substantial interference and delay in the patent issue process. See Changes to Implement Patent Term Adjustment under Twenty-Year Patent Term, 65 Fed. Reg. 56365, 56373 (Sept. 18, 2000); 1239 Off. Gaz. Pat. Office 14, 19-20 (Oct. 3, 2000) (final rule).

It should be noted, however, that only certain papers (not all papers), filed after a "Notice of Allowance" is mailed, cause substantial interference and delay in the patent issue process. Therefore, it is the filing of these papers that will be considered a "failure to engage in reasonable efforts" to conclude processing and examination of an application under 37 CFR 1.704. The Office has reviewed many allowed applications (mostly continued prosecution applications (CPAs)) that were filed on or after May 29, 2000, in which the issue fee was paid. The review consistently showed that only certain papers submitted after a "Notice of Allowance" is mailed, interfered with and delayed the patent issue process to such a degree as to constitute a "failure to engage in reasonable efforts" to conclude processing or examination of an application.

Accordingly, the Office is publishing this notice to provide guidance in interpreting the provisions of 37 CFR 1.704(c)(10) to clarify that submission of certain papers after a "Notice of Allowance," which do not cause substantial interference and delay in the patent issue process, are not considered a "failure to engage in reasonable efforts" to conclude processing or examination of an application. The following are examples of such papers: (1) Issue Fee Transmittal (PTOL-85B), (2) Power of Attorney, (3) Power to Inspect, (4) Change of Address, (5) Change of Status (small/not small entity status), (6) a response to the examiner's reasons for allowance, and (7) letters related to government interests (e.g., those between NASA and the Office). Therefore, the submission of these papers after a Notice of Allowance will not be considered a "failure to engage in reasonable efforts" to conclude processing or examination of an application and would not result in reduction of a patent term adjustment pursuant to 37 CFR 1.704(c)(10).

In contrast, the submission of other papers after a "Notice of Allowance" is mailed that do cause substantial interference and

delay in the patent issue process are considered a "failure to engage in reasonable efforts" to conclude processing or examination of an application pursuant to 37 CFR 1.704(c)(10). The following are examples of such papers: (1) a request for a refund, (2) a status letter, (3) amendments under 37 CFR 1.312, (4) late priority claims, (5) a certified copy of a priority document, (6) drawings, (7) letters related to biological deposits, and (8) oaths or declarations.

As guidance for minimizing reductions to any patent term adjustment, applicants should adopt practices that do not delay processing of the applications after the "Notice of Allowance" has been mailed. For instance, instead of filing corrected drawings or editorial amendments after the application has been allowed, applicant should submit such corrected drawings or editorial amendments prior to allowance of the application. In addition, instead of filing a status letter, applicant should use the private Patent Application Information Retrieval (PAIR) system to determine the status of the application (http://pair-direct.uspto.gov) or call the Office.

The Patent Application Locating and Monitoring (PALM) system maintains computerized contents records of all patent applications and reexaminations. PAIR is a system that provides public access to PALM for patents and applications that have been published (i.e., information for applications maintained in confidence cannot be obtained), which can be accessed over the Internet at http://pair.uspto.gov. The private side of PAIR at http://pair-direct.uspto.gov can be used by an applicant to access confidential information about his or her pending application. To access the private side of PAIR, a customer number must be associated with the correspondence address for the application, and the user of the system must have a digital certificate. For further information, contact the Customer Support Center of the Electronic Business Center at (703) 305-3028.

In addition, if PAIR is used to see the PALM records that are relied upon for patent term adjustment purposes, a contents entry with the contents code "DRWS" and the contents description "DRAWING REQUIREMENTS SATISFIED" does not indicate when the drawings were filed and is not a PALM entry that is used in the patent term adjustment calculation.

Any questions or comments about this change should be directed to Karin Tyson, Senior Legal Advisor, Office of Patent Legal Administration, Office of the Deputy Commissioner for Patent Examination Policy. Ms. Tyson can be reached by telephone at (703) 306-3159, or by e-mail at Karin.Tyson@uspto.gov.

May 29, 2001

NICHOLAS P. GODICI
Acting Under Secretary of
Commerce for Intellectual Property and
Acting Director of the United States
Patent and Trademark Office

Printer Friendly

10/692,738 N-SUBSTITUTED PYRAZOLE-O-GLYCOSIDE DERIVATIVES AND THERAPEUTIC AGENT FOR DIABETES CONTAINING THE SAME

Transaction History

| Date | Contents Description |
|---|---|
| 06-21-2005 | Recordation of Patent Grant Mailed |
| 06-01-2005 | Issue Notification Mailed |
| 06-21-2005 | Patent Issue Date Used in PTA Calculation |
| 05-19-2005 | Receipt into Pubs |
| 05-18-2005 | Dispatch to FDC |
| 05-18-2005 | Application Is Considered Ready for Issue |
| 05-09-2005 | Issue Fee Payment Verified |
| 05-05-2005 | Miscellaneous Incoming Letter |
| 05-09-2005 | Issue Fee Payment Received |
| 03-14-2005 | Workflow - File Sent to Contractor |
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| 02-07-2005 | Notice of Allowability |
| 01-25-2005 | Case Docketed to Examiner in GAU |
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| 01-27-2004 | Information Disclosure Statement (IDS) Filed |
| 01-21-2003 | Preliminary Amendment |
| 12-19-2003 | Preliminary Amendment |
| 10-27-2003 | Preliminary Amendment |
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| 02-23-2004 | Application Return from OIPE |
| 02-23-2004 | Application Return TO OIPE |
| 02-23-2004 | Application Dispatched from OIPE |
| 02-23-2004 | Application Is Now Complete |
| 02-09-2004 | Cleared by OIPE CSR |
| 12-27-2003 | IFW Scan & PACR Auto Security Review |
| 10-27-2003 | Initial Exam Team nn |

Close Window

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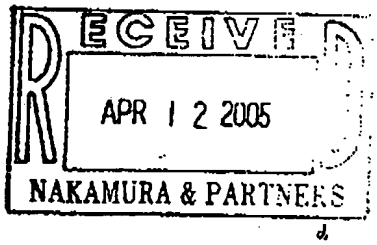


7 April 2005

Dear Mr Hakoda

**European Patent Application No: 02722839.4**
**Applicant: Ajinomoto Co., Inc.**
**Your Ref: OP 03105-2**
**Our Ref: KMN/FP6187793**

We have now received the supplementary European search report for this application and two copies are enclosed together with two copies of the single citation.

We have not yet studied the reference, but would be happy to do so, and provide you with comments if you wish. Because of its filing date it can be used to assess at most the novelty, not inventive step, of the present application.

It is not necessary to make any reply to the search report. Now that the supplementary search report has issued, it remains possible to file voluntary amendments to the application, for instance in view of the prior art cited here or elsewhere. It is also possible to file comments on the reference to put the application into good order for substantive examination. Please let us know if you wish to do either of these things.

Since the examination fee has already been paid, we will shortly be invited by the EPO to confirm that this application is to proceed to substantive examination. We will be writing again about that.

Yours sincerely

Pauline Edwards

P.P. Dr Kathryn Nicholls
for MEWBURN ELLIS LLP
kathryn.nicholls@mewburn.com

Enc: Two copies of supplementary search report
Two copies of reference

KMN/pae

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(1895 ~1973)

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81-3-3214-6359 (G-II & G-III)

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May 2, 2005
(Via Fax & Mail/ e-mail)

CONFIRMATION

VRS
1FOEC
5/9

Attention: Mr. Stephen G. Baxter

Re: U.S. Patent Appln. No. 10/692,738
Assignee: Ajinomoto Co., Inc.
Your Ref.: 244118US-1636-10-0 CONT
Our File: OP 03105-1

Dear Mr. Baxter:

This is a follow-up to our letter dated April 8, 2005. Also, we received with thanks your facsimile letter dated April 13, 2005 reporting us the completion of your file review.

As the result of our study of REASON'S FOR ALLOWANCE, we would like to inform you that the Examiner's comments are reasonable.

Also, we appreciate your kind proposal whether the accuracy of the 44-day term adjustment should be confirmed, however, we would like to say that it is NOT necessary.

On the other hand, we are enclosing herewith the supplemental European Search Report issued for the corresponding EP application. The prior art reference cited therein, EP 1 364 957 A for itself has not been submitted to the USPTO, but its patent family member, WO 02068439 A has already been submitted. In addition, we can find the Examiner's initial on WO 02068439 A appearing in the IDS sheet attached to *Notice of Allowability*. Thus, we consider that EP 1 364 957 A is not first cited in the Supplementary European Search Report and it does not put any workloads on the Examiner.

RECEIVED IN CHEM
05.09.05

10/692,738
Entered

Please file the supplemental European search report as the IDS and pay issue fee by the due date, May 9, 2005. Our client does NOT wish to FILE an additional continuation or divisional application at the present stage. In this respect, however, to file the IDS, we rely on you to take a necessary step by, for example, filing a petition or an appropriate continuation application for safety reason.

If you need further information, please feel free to contact us.

Very truly yours,

Atsushi HAKODA

AH/NM/--
Encl.: copy of supplemental European Search Report
electrical data by e-mail (EP 1364957)

P.S. Please check your file to find out whether you have already sent us all debit notes in connection with the above-identified application and have any outstanding debit note from those. If you find any such debit note, please let us know when to forward the Letters Patent.

Please acknowledge receipt by return facsimile.

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TX 31651 epo nl
FAX +31 70 340 3016

**Europäisches Patentamt**
Zweigstelle in Den Haag Recherchen-abteilung

**European Patent Office**
Branch at The Hague Search division

**Office européen des brevets**
Département à La Haye Division de la recherche

Nicholls, Kathryn Margaret
Mewburn Ellis LLP
York House
23 Kingsway
London WC2B 6HP
GRANDE BRETAGNE



GH

Datum/Date
30.03.05

| Zeichen/Réf./Réf. | Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°. |
|---|---|
| KMN/FP6187793 | 02722839.4-2101-JP0204238 |

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
Ajinomoto Co., Inc.

# COMMUNICATION

The European Patent Office herewith transmits as an enclosure the European search report for the above-mentioned European patent application.

If applicable, copies of the documents cited in the European search report are attached.

☒ Additional set(s) of copies of the documents cited in the European search report is (are) enclosed as well.

## REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

European Patent Office

# SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 02 72 2839

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.7) |
|---|---|---|---|
| E | EP 1 364 957 A (KISSEI PHARMACEUTICAL CO., LTD) 26 November 2003 (2003-11-26)<br>* page 37 - page 39 *<br>----- | 1 | C07H17/02<br>A61K31/7056<br>A61P3/10 |

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07H
A61K

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

1

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| Munich | 18 March 2005 | Bardili, W |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C04)

# ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 72 2839

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-03-2005

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 1364957 A | 26-11-2003 | CA 2438593 A1 | 06-09-2002 |
| | | EP 1364957 A1 | 26-11-2003 |
| | | US 2004132669 A1 | 08-07-2004 |
| | | WO 02068439 A1 | 06-09-2002 |
| | | TW 593329 B | 21-06-2004 |

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 364 957 A1

# (12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
**26.11.2003 Bulletin 2003/48**

(21) Application number: **02703897.5**

(22) Date of filing: **26.02.2002**

(51) Int Cl.[7]: **C07H 17/02**, C07D 233/70, C07D 417/10, C07D 401/10, A61K 31/7056, A61K 31/706, A61P 43/00, A61P 3/10, A61P 3/04, A61P 3/06, A61P 9/10, A61P 9/12, A61P 9/04, A61P 7/10, A61P 19/06

(86) International application number:
**PCT/JP02/01707**

(87) International publication number:
**WO 02/068439 (06.09.2002 Gazette 2002/36)**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR**
Designated Extension States:
**AL LT LV MK RO SI**

(30) Priority: **26.02.2001 JP 2001051278**
**27.02.2001 JP 2001052903**

(71) Applicant: **Kissei Pharmaceutical Co., Ltd.**
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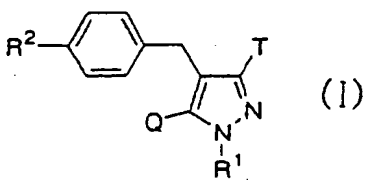
**London WC1X 8BT (GB)**

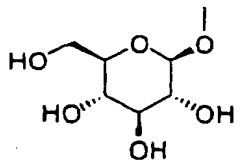
## (54) GLYCOPYRANOSYLOXYPYRAZOLE DERIVATIVES AND MEDICINAL USE THEREOF

(57) The present invention provides glucopyranosyloxypyrazole derivatives represented by the general formula:



(I)

wherein one of Q and T represents a group represented by the general formula:



while the other represents a lower alkyl group or a halo (lower alkyl) group; $R^1$ represents a hydrogen atom, an optionally substituted lower alkyl group, a lower alkenyl group, a cyclic lower alkyl group, etc.; $R^2$ represents a hydrogen atom, an optionally substituted lower alkyl group, a lower alkoxy group, a lower alkenyl group, a cyclic lower alkyl group, a cyclic lower alkoxy group, etc., which exert an excellent inhibitory activity in human SGLT2, and therefore are useful as drugs for the prevention or treatment of a disease associated with hyper-

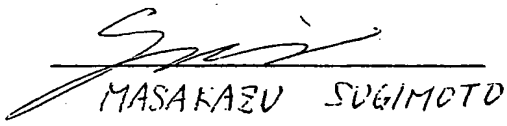
EP 1 364 957 A1

## Declaration

The standard protocol by which Ajinomoto Co., Inc. conducts prosecution of patent applications is as follows. First, Ajinomoto Co., Inc. retains one of many private local (i.e., Japanese) law firms to which the application is provided. This law firm then provides the application to firms in a national stage venue to which an application is to be pursued. These law firms in the national stage venue prosecute the application in accordance with local custom, practice, and laws, while reporting developments directly to the selected Japanese law firm. Ajinomoto Co., Inc. then receives these updates from the Japanese law firm. In the present application, the protocol above was followed.

Specifically, Ajinomoto Co., Inc. retained Nakamura & Partners (Tokyo, Japan) to manage the technology related to the present application (U.S. 10/692,738). Nakamura & Partners, in turn, provided this application to Mewburn Ellis, LLP (London, England) to prosecute the corresponding European application (EP 02 72 2839). Upon receipt of any correspondence from the European Patent Office in relation to EP 02 72 2839, including the supplementary European Search Report dated March 30, 2005, Mewburn Ellis, LLP forwards the same to Nakamura & Partners. Subsequently, Nakamura & Partners forward the correspondence and attachments received from Mewburn Ellis, LLP to Ajinomoto Co., Inc. As evidenced by the enclosed copy of the correspondence from Nakamura & Partners, the supplementary European Search Report dated March 30, 2005, was received by Ajinomoto Co., Inc. on May 10, 2005. The records of Ajinomoto Co., Inc. further reveal that there was no prior communication received relating to the supplementary European Search Report dated March 30, 2005

Ajinomoto Co., Inc has authorized Nakamura & Partners to file foreign corresponding office actions as IDS to USPTO automatically. This is the reason why the IDS has been field before the actual notice to Ajinomoto Co., Inc.



August 19, 2005

MASAKAZU SUGIMOTO
Manager
Intellectual Property Department
Ajinomoto Co., Inc.

2005年5月2日

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事　務：大元

| 部長 | | 課長 | 担当者 |
|---|---|---|---|
| | | IPC 05.5.10 杉本 | IPC 05.6.11 箱 | IPC 05.5.10 箱田 |

事件の表示
国　　名：　ＥＰＣ
種　　別：　特許
出願番号：　０２７２２８３９．４
名　　称：　Ｎ－置換ピラゾール－Ｏ－グリコシド誘導体及び
　　それらを含有する糖尿病治療薬
貴社整理番号：Ｂ－９４５
当所整理番号：ＯＰ０３１０５－２

前略　首記の件につき、欧州特許庁より追加の調査報告書（Supplementary European Search Report）が発行されました。

調査報告書について　（COMMUNICATION-RULE 86 EPC）

ここに同封した書類は、本願について欧州特許庁から発行された欧州調査報告書（EUROPEAN SEARCH REPORT）に係わるものです。これについて若干の説明を加えますと、

(1) 調査報告は、本願の明細書及び図面を考慮したうえで、クレームを基礎にして作成され、調査報告作成時点においてＥＰＯ（欧州特許庁）が利用することができる文献のうち、新規性及び進歩性に関する決定を行う際に検討の対象となりうる文献を掲げるもので、引用文献とともに出願人に送付されるものです。ただし、この調査報告には理由は付されず、また、発明の特許性に関する見解も示されません。

(2) この調査報告をうけた後、出願人は、この報告に掲げられた引用文献に照らし、自発的に明細書、クレーム及び図面の補正をすることができます。（ただし、審査部から最初の通知書を受けるまで）。

よって、もしクレーム訂正等をご希望の場合は、早い機会にその旨ご連絡下さい。
特段のご指示を戴かない場合は補正不要と了解させて頂きます。

草々

本件に関する貴殿からのご書状には、すべて上記事件の表示を付記下さいますようお願い致します。

Mewburn Ellis
LLP

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European Trade Mark Attorneys
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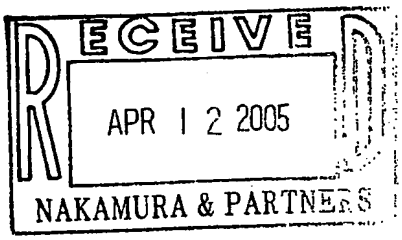


7 April 2005

Dear Mr Hakoda

**European Patent Application No: 02722839.4**
**Applicant: Ajinomoto Co., Inc.**
**Your Ref: OP 03105-2**
**Our Ref: KMN/FP6187793**

We have now received the supplementary European search report for this application and two copies are enclosed together with two copies of the single citation.

We have not yet studied the reference, but would be happy to do so, and provide you with comments if you wish. Because of its filing date it can be used to assess at most the novelty, not inventive step, of the present application.

It is not necessary to make any reply to the search report. Now that the supplementary search report has issued, it remains possible to file voluntary amendments to the application, for instance in view of the prior art cited here or elsewhere. It is also possible to file comments on the reference to put the application into good order for substantive examination. Please let us know if you wish to do either of these things.

Since the examination fee has already been paid, we will shortly be invited by the EPO to confirm that this application is to proceed to substantive examination. We will be writing again about that.

Yours sincerely

Dr Kathryn Nicholls
for MEWBURN ELLIS LLP
kathryn.nicholls@mewburn.com

Enc: Two copies of supplementary search report
Two copies of reference

KMN/pae

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Datum/Date
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| Zeichen/Réf./Réf. | Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°. |
|---|---|
| KMN/FP6187793 | 02722839.4-2101-JP0204238 |

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
Ajinomoto Co., Inc.

# COMMUNICATION

The European Patent Office herewith transmits as an enclosure the European search report for the above-mentioned European patent application.

If applicable, copies of the documents cited in the European search report are attached.

☒ Additional set(s) of copies of the documents cited in the European search report is (are) enclosed as well.

## REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

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